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EXOPHTHALMOS OF GRAVES' DISEASE: A SUMMARY OF THE PRESENT STATUS OF THERAPY *

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GRAVES' disease may be considered to be a thyroid-pituitary syndrome. The two chief manifestations of the disorder are exophthalmos and hyperplastic goiter with hyperthyroidism. They usually are concurrent but may be totally dissociated, either one preceding the other. Sometimes exophthalmos is the only manifestation of the disease.

In Graves' disease the term *exophthalmos* designates not only proptosis but also various associated manifestations, such as lid retraction and other changes associated with increase in bulk of the periocular tissues. This increase is due to increase in fat and in mucopolysaccharides, and sometimes to apparent edema, although the studies of Rundle and associates [1, 2] showed that there is no increase in the water content of the tissues involved in exophthalmos. The extraocular muscles enlarge, appearing to be edematous, and are infiltrated with fat and lymphocytes; paralysis and fibrosis of these muscles subsequently develop. The proptosis may be extreme, with little swelling of the lids and conjunctivae, or the lids and conjunctivae may be extremely swollen, with relatively little proptosis. Bothersome ocular symptoms commonly include a burning sensation, pain, lacrimation and diplopia, especially on upward gaze. Exophthalmos usually subsides after

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control of the hyperthyroidism, but in about 40% of patients it fails to improve or becomes worse, and in about 1% it may become extremely severe.

Exophthalmos is believed to be caused by an excess of thyroid-stimulating hormone or of a closely related material called *exophthalmos-producing substance.*[3,4] Attempts at reducing exophthalmos, with the exception of orbital decompression, have been primarily designed to suppress pituitary hyperactivity. Because in many instances there is a gradual tendency to spontaneous improvement, it is often difficult if not impossible to ascribe with certainty improvement to the therapy.

The purpose of this paper is to comment on the treatment of exophthalmos, chiefly in relation to some of our own results.

Iodine

Iodine has been used rather extensively in the past in attempts to modify the exophthalmos of Graves' disease, largely on the basis of demonstrations that under certain experimental conditions thyroid-stimulating hormone may be inactivated by the action of iodine.[5] The paucity of reports of good results would seem to indicate the inefficiency of this method clinically.

Estrogens and Androgens

Estrogens are for the most part powerful inhibitors of the production of the hormones of the anterior pituitary, especially of the gonadotropins, but to some extent of other pituitary hormones also. Androgens are less powerful in this respect. Both steroids have been used in attempts to reduce exophthalmos but, so far as we are aware, have produced no impressively favorable results. Unfortunately, each of these steroids has a moderately powerful sodium- and water-retaining effect, as well as other effects that are undesirable in a patient with exophthalmos.

Roentgen Therapy

Roentgen irradiation, usually in doses of 2,000 to 4,000 r at the surface, has been applied to the pituitary region for the treatment of exophthalmos. Improvement generally has been absent, slight or not reproducible, and decreases in proptosis of more than 3 mm. are rare and often so very gradual that they cannot be readily ascribed to the treatment.

In 1946 we [6] reported the results of roentgen therapy in 13 patients with exophthalmos, five men and eight women. One of the five men showed significant improvement, that is, a recession of proptosis of 3 mm. in one eye and of 5 mm. in the other eye over a period of 17 months, and two of the eight women showed improvement. We considered these results to be rather unencouraging.

Beierwaltes [7] reviewed the results of roentgen therapy in 28 patients,

eight of whom showed a recession of proptosis averaging 2 mm. or more. The improvement for the most part began within seven months after treatment. In one patient there was a dramatic response (a 15-mm. recession in proptosis), but it was not noted until 24 months after treatment.

Lamberg [8] recently presented an extensive review of roentgen therapy for exophthalmos and reported the results of treatment in 38 patients. It is interesting to note that this treatment produced a favorable effect (a 2-mm.

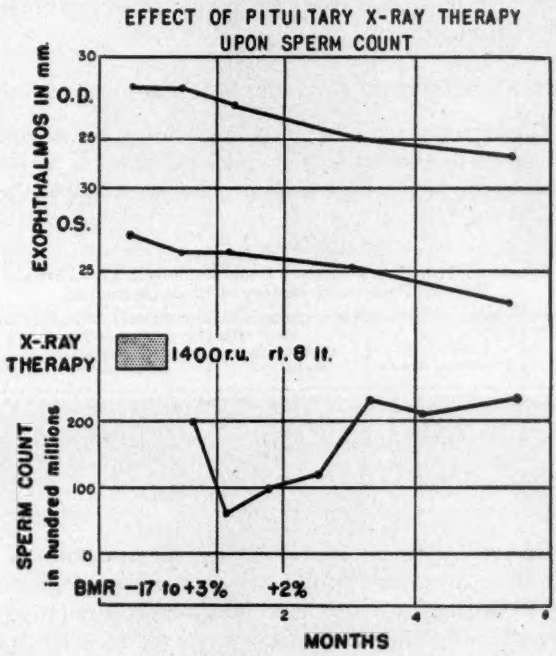

FIG. 1. Note the effect of roentgen therapy to pituitary upon the sperm count, used as an assay method. The effect apparently disappeared within two months.

recession in proptosis in one eye) in only two of 23 patients with postthyroidectomy exophthalmos. Of 13 patients receiving antithyroid drugs who were given roentgen therapy for exophthalmos, five had a recession of proptosis of 2 mm. or more in one eye. These patients presumably were recovering from hyperthyroidism, a period during which a majority of patients show improvement in exophthalmos without other therapy. For example, after I^{181} therapy, Werner [9] observed improvement in 45 (64%) of 71 patients with infiltrative exophthalmos, and Clark [10] observed improvement in 34 (55%) of 62 patients. Sloan [11] found that improvement in exophthalmos occurred after thyroidectomy in 57% of 100 patients.

Our own confidence in roentgen therapy is reduced considerably by the following facts:

1. Doses of roentgen irradiation of as high as 10,000 r have not produced measurable hypopituitarism.[12]

2. Changes in other pituitary hormones, as determined by assays [13] or by sperm counts (figure 1) [6] following such treatment, have been evanescent.

3. Improvement that has occurred is often relatively insignificant, amounting to less than a 1.5-mm. recession of proptosis.

4. Improvement in some patients has not occurred until months or even years after treatment.

Desiccated Thyroid, Thyroxin or Tri-iodothyronine

It has been common practice to give enough desiccated thyroid to patients with exophthalmos to prevent hypothyroidism, or even to prevent hypometabolism not clearly thyroidal in origin. This procedure has been followed

Table 1

Effect of l-Tri-iodothyronine on Exophthalmos in Five Patients Without Presence or History of Hyperthyroidism

Case No.	Duration of Treatment, months	l-Tri-iodothyronine, μg. per day	Duration of Exophthalmos	Recession of Proptosis of 2 mm. or More
1	3	100	5 mo.	Yes
2	4	100	2 mo.	Yes
3	6	100	1 yr. 9 mo.	No
4	6	75	3 yr. 3 mo.	No
5	10	100	7 mo.	Yes

in the hope of preventing or decreasing hyperpituitarism. In some cases doses of thyroid or thyroxin that are larger than physiologic amounts have been used in an attempt to reduce exophthalmos, but improvement usually has been clinically insignificant or temporary. We have no data to suggest that tri-iodothyronine is more effective than desiccated thyroid or thyroxin, since the two latter agents may have been used in the past in insufficient doses or for insufficient periods of time.

We have made repeated observations on 20 patients with progressive exophthalmos treated with tri-iodothyronine over periods ranging from two to 11 months. In this period of time proptosis was reduced by 2 mm. or more in nine patients, remained stationary in nine, and became worse in two. The aim was to give l-tri-iodothyronine in the largest dosage that the patient could tolerate with comfort, usually 100 μg. per day (range, 75 to 200 μg. per day). Six of the nine patients showing significant recession did so at their first visit, two months after beginning treatment.

The results in five patients without hyperthyroidism who received l-tri-iodothyronine are summarized in table 1. In these patients before admin-

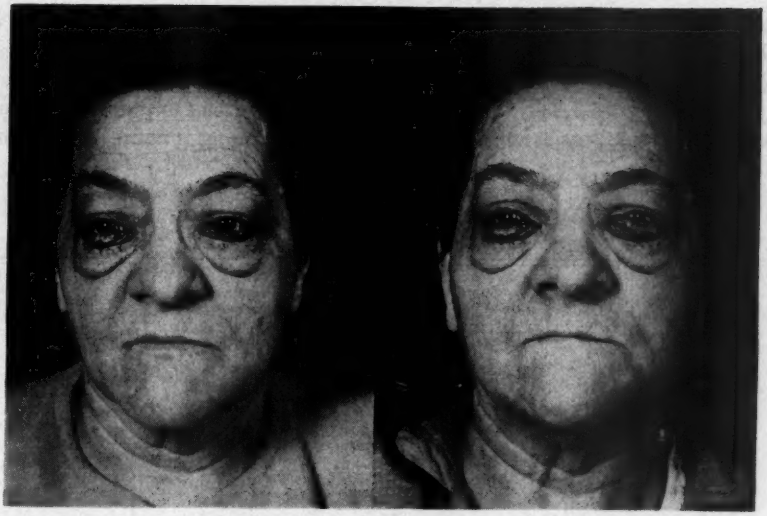

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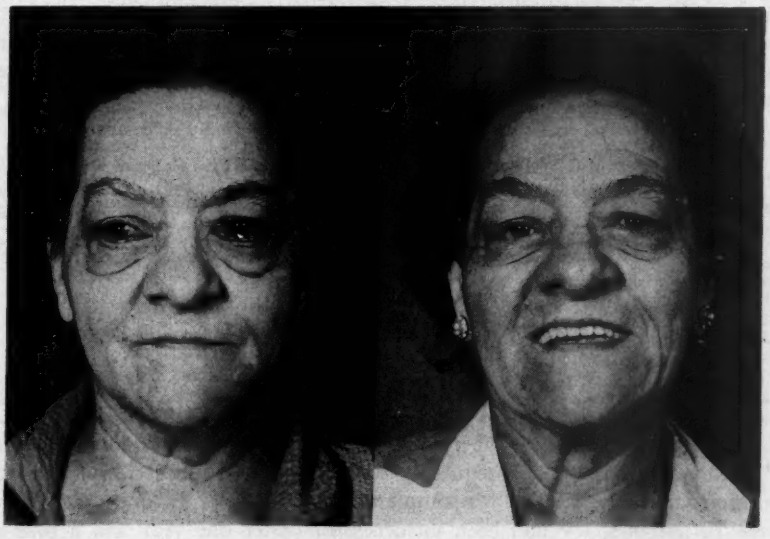
FIG. 2. *Case 2.* A. Photograph of patient having marked soft-tissue swelling. B. Photograph of patient taken one week after that shown in A and prior to treatment. Note rapidity of progression of the changes.



A B

FIG. 3. *Case 2.* A. Photograph of patient after three weeks of therapy with l-tri-iodothyronine, 100 μg. per day. B. Photograph of patient four months after beginning of tri-iodothyronine therapy, showing marked diminution of soft-tissue swelling. Vision had improved greatly.

istration of thyroid hormone, I^{131} * uptake was normal, ranging from 11 to 49% in six to 24 hours. The most striking changes were seen in a 69 year old woman (case 2) in whom there was no evidence or history of hyperthyroidism (figure 2A). She was totally blind, and had extreme soft-tissue swelling and proptosis which were rapidly worsening (figure 2B). Improvement was evident in a few days after treatment had been started, and was pronounced in three weeks (figure 3A). Later, there were almost complete disappearance of the lid and conjunctival swelling, 5 and 6 mm. recession in proptosis, and recovery of vision from complete blindness to fairly good eyesight. Ninety per cent of these changes occurred within three months (figure 3B).

TABLE 2

Effect of l-Tri-iodothyronine on Exophthalmos in 10 Patients With Hyperthyroidism Treated with I^{131}

Case No.	Duration of Treatment, months	l-Tri-iodothyronine, μg. per day	Duration of Exophthalmos	Recession of Proptosis of 2 mm. or More
6	2	75	8 mo.	No
7	3	75	7 yr.	No
8	3	100	11 mo.	Yes
9	4	75	1 yr. 1 mo.	Yes
10	6	100	3 yr. 8 mo.	No
11	6	50–100	1 yr. 3 mo.	No
12	6	100	3 yr. 1 mo.	Yes
13	9	25–75	1 yr. 3 mo.	No
14	11	50–100	1 yr. 4 mo.	No
15	11	75	1 yr. 6 mo.	Yes

TABLE 3

Effect of l-Tri-iodothyronine on Exophthalmos in Five Patients With Hyperthyroidism Treated with Propylthiouracil

Case No.	Duration of Treatment, months	l-Tri-iodothyronine, μg. per day	Duration of Exophthalmos	Recession of Proptosis of 2 mm. or More
16	2	50–75	5 mo.	No
17	6	50	2 mo.	No
18	7	50–75	10 yr. 3 mo.	No
19	10	75–100	4 yr.	Yes
20	11	100	9 mo.	Yes

In 10 patients having hyperthyroidism treated by the administration of I^{131}, exophthalmos was subsequently treated by the administration of l-tri-iodothyronine; the results are summarized in table 2. In one (case 7) of these 10 patients, I^{131} had been unsuccessful (after one year and a total of 93 mc. of I^{131}) and thyroidectomy had been performed.

* The radioactive material used in this investigation was supplied by Abbott Laboratories on the authorization of the Isotopes Division, U. S. Atomic Energy Commission, Oak Ridge, Tennessee.

TABLE 4

Findings in Patient (Case 21) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings						Treatment			
	Exophthalmometric Measurements, mm.		BMR, %	PBI, μg. per 100 ml.	Cholesterol, mg./100 ml.	24-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	l-Tri-iodothyronine, μg. per day	I^{131}, mc.
	OD	OS								
12-6-56	29	15	+34	9	—	75	—	—	—	—
12-13	30	15	+18	—	183	70	—	—	100	—
12-18	—	—	—	—	—	73	—	—	75	3.0
1-3-57	29	18	+17	3	—	—	—	—	—	—
1-14	30	20	+7	—	180	—	40	200	—	—
1-15	28	20	—	—	—	—	40	200	—	—
1-21	25	19	+4	—	260	—	40	200	—	—
1-28	—	—	—	—	—	—	—	160	—	—
2-15	27.5	21	−1	1	162	—	—	160	100	—
2-28	28	21	—	—	—	10	—	80	100	—
4-19	27	19.5	—	—	—	—	—	80	100	—

In five patients hyperthyroidism was successfully treated with propylthiouracil, and subsequently exophthalmos was treated with l-tri-iodothyronine. The duration of the exophthalmos ranged from two months to 10 years, and the duration of treatment with tri-iodothyronine ranged from two to 11 months. The results are summarized in table 3.

TABLE 5

Findings in Patient (Case 22) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings						Treatment		
	Exophthalmometric Measurements, mm.		BMR, %	PBI, μg. per 100 ml.	Cholesterol, mg./100 ml.	24-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	l-Tri-iodothyronine, μg. per day
	OD	OS							
12-14-56	28	26	+28	—	143	96	40	200	—
12-17	—	—	—	—	—	73	40	200	—
12-19	27	26	+6	5	—	—	40	200	—
12-20	—	—	—	—	—	—	40	150	—
12-21	27.5	26	—	—	—	—	20	150	—
12-22	—	—	—	—	—	—	20	125	—
12-24	27	25.5	—	3	—	—	—	125	—
12-26	27	25.5	—	—	—	82	—	100	—
12-30	—	—	—	—	—	—	—	60	—
1-1-57	26	25	—	—	—	—	—	60	—
1-22	—	—	−10	5	276	79	—	60	—
1-25	25	24	—	—	229	—	40	60	—
1-29	24	24	—	—	—	—	—	60	50–75
2-25	25	25	+10	—	—	35	—	60	100

TABLE 6

Findings in Patient (Case 23*) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings						Treatment			
	Exophthalmometric Measurements, mm.		BMR, %	PBI, μg. per 100 ml.	Cholesterol, mg./100 ml.	6-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	l-Tri-iodothyronine, μg. per day	I^{131}, mc.
	OD	OS								
6-8-55	26	26	+27	—	162	89	—	—	—	10
8-26	26	25.5	+52	—	—	95	—	—	—	20
11-1	27	25	+26	—	—	95	—	—	—	10
1-12-56	28	26	+19	—	—	64	—	—	—	10
3-8	27	26.5	−4	—	—	TSH: 27→40	—	—	50–100	—
7-2	32	28	+2	—	—	34	—	—	100	6
10-2	30	28	−3	—	—	34	—	—	150	—
2-5-57	31	28	+2	5	135	24	40	200	150	—
2-14	30	27	+4	2	117	20	20	100	150	—
3-12	31	28	−2	2	165	24	—	80	150	—
4-24	31	30	−3	—	94	18	—	30	150	—

* Also listed as case 14.

ACTH AND CORTISONE OR HYDROCORTISONE

Since 1950 various attempts have been made to treat exophthalmos with ACTH and with cortisone or hydrocortisone locally or systemically.[14] Early trials were not very promising, but in 1953 Kinsell [15] reported encouraging results in nine patients who received large doses of ACTH and cortisone, some of whom were followed for two years. Improvement occurred in all nine patients, but there were two serious complications—temporary psychosis in one, and perforated peptic ulcer in another. In 1955, findings in 28 patients, five of whom received ACTH and 23 of whom received corti-

TABLE 7

Findings in Patient (Case 24) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings						Treatment			
	Exophthalmometric Measurements, mm.		BMR, %	PBI, μg. per 100 ml.	Choiesterol, mg./100 ml.	6-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	l-Tri-iodothyronine, μg. per day	I^{131}, mc.
	OD	OS								
2-16-57	26	26.5	+19	7	215	32	40	200	—	—
2-18	—	—	+20	—	203	—	40	200	—	—
2-19	26	26	—	—	—	—	40	200	—	6
2-21	—	—	—	—	—	—	—	160	50	—
3-12	26	25	+14	6	171	—	—	120	50	—
4-24	25	27	+3	—	—	25	—	60	100	—

TABLE 8

Findings in Patient (Case 25) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings						Treatment			
	Exophthalmometric Measurements, mm.		BMR, %	PBI, μg. per 100 ml.	Cholesterol, mg./100 ml.	24-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	l-Tri-iodothyronine, μg. per day	Propylthiouracil, mg./day
	OD	OS								
10-2-56	26	25	+11	4	209	73	—	—	—	300
1-8-57	26	24	−8	—	—	—	—	—	—	300
1-24	26.5	25	−12	—	129	49	40	200	—	—
2-1	—	—	−15	—	124	21	40	200	—	—
2-5	—	—	—	—	—	—	30	180	—	—
2-6	27	26	—	—	—	—	—	160	—	—
2-7	—	—	—	—	—	—	—	120	—	—
3-7	26	25	−29	—	225	50	—	120	75–100	—
5-7	26	26	−9	—	—	11	—	60	100	—

sone, mostly in relatively small doses, were reported in England.[16] Eight of the 28 patients showed moderate to marked improvement.

We have treated 10 patients with both ACTH and hydrocortisone. Each patient received 50 mg. of ACTH intravenously for a period of six hours daily for from five to 16 days, and 200 mg. of hydrocortisone orally daily; the dosage of the latter drug was diminished over a period of weeks. Some patients initially received ACTH alone for from one to two weeks, and then orally administered cortisone or hydrocortisone was added to the thera-

TABLE 9

Findings in Patient (Case 26*) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings					Treatment			
	Exophthalmometric Measurements, mm.		BMR, %	Cholesterol, mg./100 ml.	24-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	l-Tri-iodothyronine, μg. per day	Thyroid, gr./day
	OD	OS							
7-21-53	23	24	−9	155	50	—	—	—	—
12-8	—	—	—	—	62	—	—	—	2
12-13	28	27	−6	174	62	—	—	—	2
4-26-54	29	29	+3	130	56	—	—	—	2
11-22	25.5	26	−8	142	30	—	—	—	2
4-21-55	28	27	+14	164	82	—	—	—	I^{131}, 3 mc.
10-4	—	—	−28	209	7	—	—	—	1½
8-31	31.5	30	−13	177	6	—	—	100	—
12-11	30	29	−11	174	12	—	—	100	—
3- 5-57	30	30.5	−13	154	7	—	—	100	—
3-17	—	—	—	—	—	40	—	—	—
3-27	30	30	−10	—	7	—	100	—	—

* Also listed as case 10.

TABLE 10

Findings in Patient (Case 27) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings					Treatment			
	Exophthalmometric Measurements, mm.		BMR, %	Cholesterol, mg./100 ml.	24-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	l-Tri-iodothyronine, μg. per day	Propylthiouracil, mg./day
	OD	OS							
3-9-57	19	20	+26	200	32	40	200	—	—
3-13	—	—	+26	232	26	40	200	—	—
3-19	20	20	+16	186	13	40	200	—	—
3-25	—	—	+7	154	—	40	200	—	—
4-1	20	21	+15	149	10	20	200	—	300
4-5	20	21	+21	174	6	40 (twice weekly)	100	—	300
4-25	20	21	+4	276	—	40 (twice weekly)	60	50	—

peutic program. Duration of follow-up ranged from one to four months. There was symptomatic improvement in all 10 patients. The sense of conjunctival irritation, lacrimation and any ocular pain that had been present usually diminished greatly or disappeared in from one to three days after treatment had been instituted. Conjunctival and lid swelling apparently diminished in all but one patient (case 26), in whom there was marked proptosis but little or no bulging or thickening of the lids apart from that caused directly by the proptosis. The findings in these 10 patients are summarized in tables 4 through 13.

There was dramatic improvement in the proptosis as well as in the soft-tissue swelling in only two of the 10 patients; it is interesting that active

TABLE 11

Findings in Patient (Case 28) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings					Treatment		
	Exophthalmometric Measurements, mm.		BMR, %	Cholesterol, mg./100 ml.	6-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone mg./day	Thyroid, gr./day
	OD	OS						
3-23-57	28–29	30	−2	272	9	40	—	—
3-27	29.5	29	−3	—	—	40	—	—
4- 1	29.5	28.5	—	160	TSH: 10→9	40	—	½
4- 4	27	27	—	—	—	40	200	½
4-11	29	28	−3	177	—	40 (twice weekly)	100	1
5- 2	28	29.5	−7	140	11	—	60	1

TABLE 12

Findings in Patient (Case 29) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings						Treatment			
	Exophthalmometric Measurements, mm.		BMR, %	PBI, μg. per 100 ml.	Cholesterol, mg./100 ml.	6-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	l-Tri-iodothyronine, μg. per day	Thyroxin, mg./day
	OD	OS								
10-21-55	25	24	−9	—	284	TSH 14→10	—	—	—	0.3
10-17-56	24	23	+6	7	253	TSH 10→11	—	—	100	—
3-22-57	24.5	22	−6	2	284	7	40	200	100	—
4-2	24	22	−1	—	168	9	40	200	100	—
4-9	24	23	+1	—	—	9	40 (twice weekly)	100	100	—
5-7	24	23	—	—	—	—	40 (weekly)	60	75	—

hyperthyroidism was present in these two patients. Brief case reports of these two patients follow.

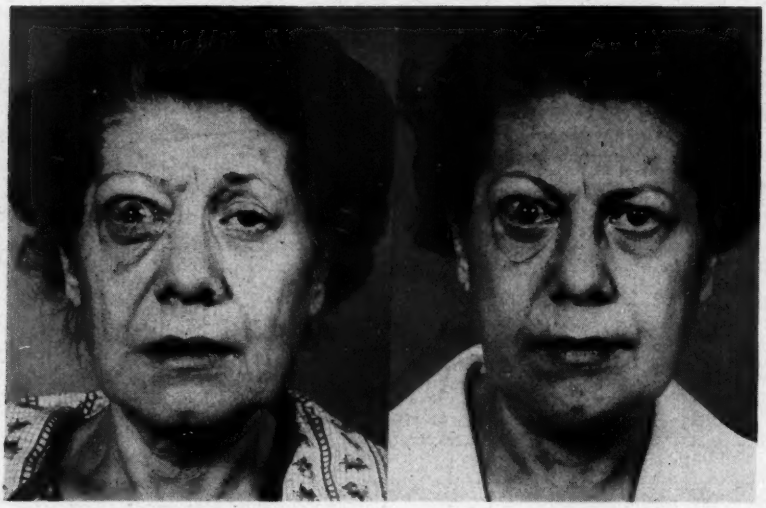
CASE REPORTS

Case 21 (table 4). A 61 year old woman had had progressive exophthalmos of the right eye for nearly one year, but hyperthyroidism apparently developed shortly before we saw her. She had lost 15 pounds in weight. The pulse rate was 100 per minute, and blood pressure was 130/70 mm. Hg. The thyroid was estimated to weigh 30 gm. She was given sedatives and l-tri-iodothyronine, 100 μg. daily for one week while hyperthyroidism was present, in an unsuccessful attempt to suppress I^{131} uptake. On December 18, 1956, the dosage of l-tri-iodothyronine was reduced to 75 μg. daily, and I^{131}, 3 mc., was administered. L-tri-iodothyronine was discon-

TABLE 13

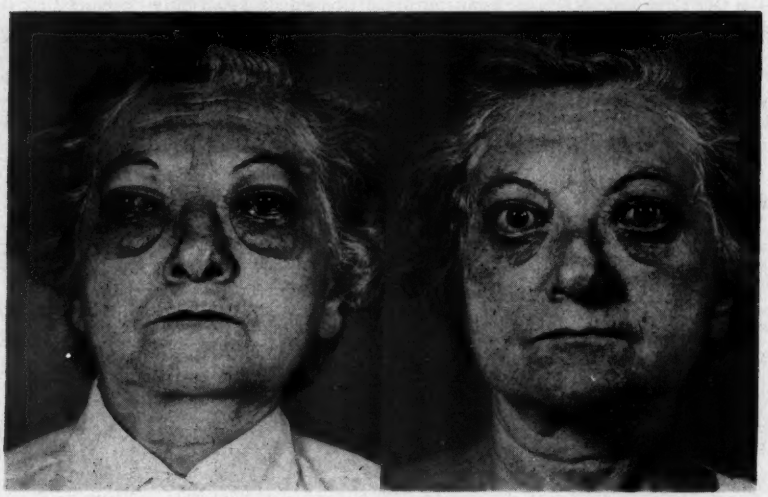
Findings in Patient (Case 30) Having Exophthalmos Treated with ACTH and Hydrocortisone

Date	Findings						Treatment		
	Exophthalmometric Measurements, mm.		BMR, %	PBI, μg. per 100 ml.	Cholesterol, mg./100 ml.	6-Hr. I^{131} Uptake, %	ACTH, mg./day	Hydrocortisone, mg./day	Propylthiouracil, mg./day
	OD	OS							
7-27-56	—	—	+58	—	—	85	—	—	150 (I^{131}, 7.0 mc.)
10-3	—	—	+60	—	—	89	—	—	150 (I^{131}, 5.0 mc.)
1-21-57	22.5	22.5	+ 4	4	246	95	—	—	—
3-13	—	—	+21	11	192	—	40	—	—
3-21	22	22	+32	15	—	—	—	120	400
4-17	—	—	—	—	—	—	—	50	400



A B

FIG. 4. *Case 21.* A. Photograph of patient having exophthalmos of Graves' disease, almost entirely unilateral, before treatment. B. Photograph of patient one month after beginning therapy, which consisted of a short course of intravenously administered ACTH, plus hydrocortisone in diminishing doses.



A B

FIG. 5. *Case 22.* A. Photograph of patient having exophthalmos of Graves' disease, with marked soft-tissue infiltration associated with hyperthyroidism. B. Photograph of patient two weeks after intravenous administration of ACTH was begun. ACTH was given for five days and hydrocortisone was given for two weeks.

tinued on January 3, 1957. Four weeks after the I^{131} therapy (January 14, 1957), the hyperthyroidism had largely disappeared but the proptosis remained 30 mm. in the right eye and had increased 5 mm. in the left eye (figure 4A) Intravenous administration of ACTH and oral administration of hydrocortisone were then begun. Within a week, in the right eye almost all of the ugly, edematous-looking red sac of conjunctiva had disappeared, much of the lid swelling was gone, and the proptosis had reduced by 5 mm. (figure 4B). In the other eye the soft-tissue changes were minimal; the proptosis in that eye had been reduced by about 1 mm. In one month, while the patient was receiving hydrocortisone and no ACTH, the proptosis again increased but the soft-tissue swelling remained greatly improved.

Case 22 (table 5). A 59 year old woman had had progressive exophthalmos for eight months. She had lost 10 pounds in weight. At the time of initial examination (December 14, 1956), the chemosis and soft-tissue swelling were extreme (figure 5A). She had typical hyperthyroidism, with a pulse rate of 108 per minute and blood pressure of 210/100 mm. Hg. The thyroid was estimated to weigh 30 gm.

The patient was given ACTH and hydrocortisone in the dosages listed in table 5. No other treatment was directed toward the hyperthyroidism. During the 10 days after treatment had been started, clinical evidence of the hyperthyroidism disappeared and the results of tests reverted to normal. During the first few days of treatment, chemosis and soft-tissue swelling were markedly reduced, and within two weeks they were almost completely gone (figure 5B). Within two and one-half months the proptosis was reduced by approximately 3 mm. in one eye and 2 mm. in the other. This improvement has so far been maintained by continued oral administration of hydrocortisone and l-tri-iodothyronine.

Tables 6 through 13 present the findings in the remaining eight patients who received ACTH and hydrocortisone. It should be noted that case 23 (table 6) had active, moderately severe hyperthyroidism that was extremely resistant to I^{131} therapy, requiring five times the usual dose for control. The exophthalmos in this patient continued to worsen during nine months of tri-iodothyronine therapy. During the ACTH-steroid treatment there was no increase in exophthalmos, although the period of observation was short. The improvement in proptosis was equivocal or absent.

Pituitary Surgery

Pituitary surgery has been performed in an attempt to reduce extremely severe exophthalmos in a few patients. Our experience with this operation extends over a period of years and involves nine patients. The only other patient who has been similarly treated of whom we are aware was reported in 1955 by Albeaux-Fernet and associates.[17] Our first patient was observed in 1937, and five of our nine patients were operated upon prior to 1946. In all nine patients the exophthalmos improved postoperatively; in some it disappeared entirely, and visual acuity that had been extremely poor returned to normal. Four of these patients (cases 31, 32, 34 and 35) were mentioned in a previous publication.[6] Pituitary surgery was abandoned because of the development in one patient (case 34) of severe pituitary deficiency with cachexia which we thought was at least partially responsible for his death; however, death did not occur for four years and seven months postopera-

tively, and necropsy revealed other possible causes of death, as mentioned below.

Recently, because of our faith in the fundamental principles involved in pituitary surgery in the treatment of exophthalmos, and because of improvement in surgical technics and, more recently, in replacement therapy for severe pituitary failure, the operation has been revived and modified.

The surgical procedures in these nine patients have included some combination of the following: section of the pituitary stalk, cauterization of the anterior lobe, and placement of an impervious diaphragm of plastic, waxed paper, or tantalum, above the sella turcica in the hope of interfering with regeneration of the "portal circulation" of the pituitary. In the first four patients who underwent pituitary surgery, unroofing of the bony orbit was performed on one side and the evaluation of improvement resulting from the pituitary surgery was based on the degree of improvement on the side that was not decompressed. We hope that simpler methods of producing hypopituitarism will be developed: the placing of radioactive materials within the sella turcica, or cobalt-60 or cyclotron irradiation to the pituitary, possibly will prove successful.

Summaries of the findings in the first five patients having exophthalmos treated by pituitary surgery are presented below (cases 31–35). These patients were operated on prior to 1946. The remainder of the patients have been operated on since 1953. The data in cases 37 and 38 are presented in detail because we wish to contrast the more rapid and greater degree of improvement in the one patient who had severe hypopituitarism after anterior pituitary cauterization with that in the other patient who had less evidence of pituitary deficiency after stalk section alone. Case 39 is mentioned only briefly because the follow-up period at the time of writing was less than two months.

Case 31. A 53 year old woman had had thyroidectomy for Graves' disease. Nine years later she was examined here because of very severe progressive exophthalmos with considerable chemosis of a few months' duration. The blood pressure was 260/160 mm. Hg. There was no hyperthyroidism.

In May, 1937, frontal craniotomy with right orbital decompression was performed; at the same time the pituitary stalk was sectioned and the anterior pituitary was cauterized in the hope of benefiting the hypertension. After operation the hypertension was not affected but the exophthalmos in both eyes disappeared. Extreme infiltrative phenomena also disappeared; representative measurements of proptosis are presented in table 14. The patient died in 1946 of other causes.

Case 32. A 49 year old man had had thyroidectomy for recurrent hyperthyroidism 30 months prior to the development of severe exophthalmos with extreme infiltrative phenomena on the left and pronounced diminution in vision. Clinically, he was euthyroid. On October 27, 1939, a left orbital decompression was performed which was inadequate because of the presence of an unusually large frontal sinus. Pituitary stalk section and anterior lobe cauterization was performed at the same time. His blood pressure preoperatively was 160/110 mm. Hg. Exophthalmometric measurements are presented in table 15. Ten months postoperatively his blood pressure was 170/110 mm. Hg. Subsequently his wife reported that he no longer had

TABLE 14

Exophthalmometric Measurements Before and After Pituitary Surgery and Right Orbital Decompression (Case 31)

Date	Exophthalmometric Measurements, mm.	
	OD	OS
12-19-36	23	24
5-17-37	Pituitary surgery and orbital decompression, exophthalmometric measurements not available	
6-16-37	Marked improvement	
6-20-37	25	23
2-14-38	22	19
11-30-38*	19	18

* Blood pressure, 250/130 mm. Hg.

hypertension. His vision was perfect. He died of a vascular accident when he was 66 years of age, 14 years after operation.

Case 33. A 52 year old man had had thyroidectomy one year prior to the development of ocular symptoms consisting of diminution in visual acuity, diplopia, and exophthalmos with extreme lid swelling. The left eye became blind, and visual acuity became markedly diminished on the right. The blood pressure was 145/100 mm. Hg.

A right frontal craniotomy with pituitary stalk section and pituitary cauterization was performed. The attending ophthalmologist noted improvement in the exophthalmos one day postoperatively, but the patient died on the third postoperative day of an intracranial hemorrhage.

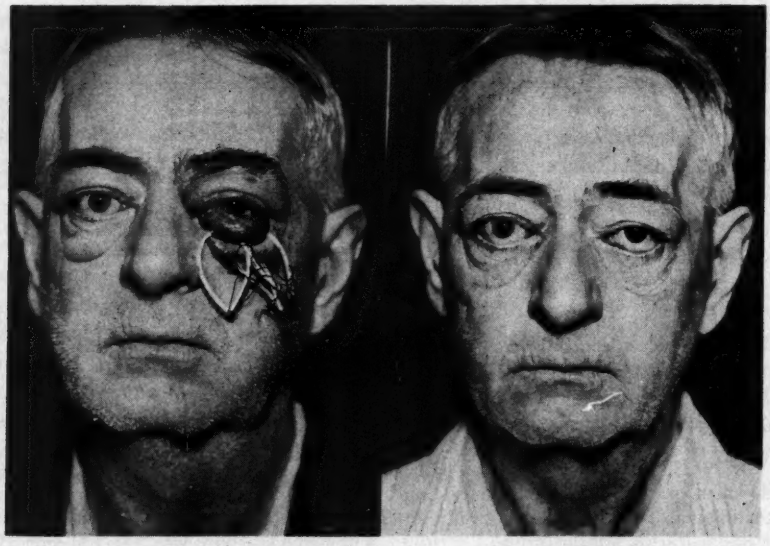
Case 34. A 58 year old man with severe exophthalmos was seen 13 months after thyroidectomy. Infiltrative phenomena were most pronounced on the left (figure 6A). The basal metabolic rate was minus 12%. A wide left orbital decompression, pituitary stalk section and pituitary cauterization were performed.

Improvement in the exophthalmos was dramatic (figure 6B). The patient developed pituitary cachexia, as indicated by low concentration of urinary follicle-stimulating hormone (FSH). The basal metabolic rate was minus 32% and there was extreme testicular atrophy, proved by biopsy. Exophthalmometric readings are reported in table 16. The improvement in his right eye was pronounced but gradual.

TABLE 15

Exophthalmometric Measurements Before and After Pituitary Surgery and Left Orbital Decompression (Case 32)

Date	Exophthalmometric Measurements, mm.	
	OD	OS
10-25-39	33	35+
10-27-39	Pituitary surgery and orbital decompression	
11-15-39	30	32
12- 4-39	Orbital swelling less—visual acuity improved	
5-15-44	30	30
1- 9-45	29	28
4-22-53	29	28



A B

FIG. 6. *Case 34.* A. Photograph of patient having severe exophthalmos with extreme soft-tissue swelling, chiefly unilateral, not associated with hyperthyroidism. Thyroidectomy had been performed eight months prior to onset of exophthalmos. B. Photograph of patient seven months after unilateral orbital decompression, plus cauterization of anterior pituitary, followed by pituitary deficiency.

The patient died elsewhere in July, 1946, four and one-half years after pituitary surgery. Autopsy showed acute pulmonary edema and chronic glomerulonephritis.

Case 35. A 61 year old man had severe exophthalmos associated with euthyroidism. He had neither history nor present evidence of hyperthyroidism. The exophthalmos did not respond to roentgen therapy to the pituitary, and one month after treatment proptosis had increased 2.5 mm. in one eye and about 2 mm. in the other.

Left orbital decompression was performed and cautery was applied to the pituitary on January 4, 1946. Preoperatively, exophthalmometric measurements were 31.5 mm. in the right eye and 29 mm. in the left; four and one-half weeks after operation they

TABLE 16

Exophthalmometric Measurements Before and After Pituitary Surgery and Left Orbital Decompression (Case 34)

Date	Exophthalmometric Measurements, mm.	
	OD	OS
11-19-41	29	30
12- 9-41	Pituitary surgery and orbital decompression	
4-27-42	29	25
6-17-42	30	25
2-11-43	28	25
11- 6-44	24	23

measured 29 mm. in the right and 24 mm. in the left. Following this the proptosis continued to recede, but vision did not improve because of permanent optic nerve damage. The patient died suddenly in October, 1953, of a probable cerebrovascular accident. Prior to his death he complained of some weakness and cold intolerance.

Case 36. A 64 year old woman had had a thyroidectomy for Graves' disease. Subsequently myxedema developed, which was treated by the administration of desiccated thyroid. Fifteen years after thyroidectomy diabetes mellitus developed, and four years later localized myxedema appeared. Twenty-three years after thyroidectomy, and two years before pituitary surgery, arterial hypertension and exophthalmos developed. Within a few months prior to pituitary surgery the exophthalmos had become extremely severe, the patient's vision was poor and papilledema was present

In September, 1953, she required 25 units of insulin per day. Her blood pressure ranged from 200/85 to 130/85 mm. Hg. On September 25, 1953, a wide bilateral orbital decompression was performed. The exophthalmos improved somewhat for six weeks postoperatively and then became even more severe than it had been before operation. By December her blood pressure was 210/100 mm. Hg. On December 9, 1953, pituitary stalk section and anterior pituitary cauterization was performed and a piece of waxed paper was placed over the sella turcica. For a few days postoperatively the patient was given ACTH and cortisone.

The extreme conjunctival and lid swelling that before operation had prevented opening of the eyes was reduced markedly within a few days after operation. Prior to operation, when the eyes were pried open she could not count fingers at 1 or 2 feet. Within two weeks postoperatively the visible swelling had decreased about 50% and she was able to see well enough to walk about her room with ease. Her daily blood pressure averaged about 160/80 mm. Hg. Insulin, 25 units per day, was still required to control hyperglycemia.

On the twenty-first postoperative day the patient developed thrombosis of the inferior mesenteric artery and gangrene of the left colon, which was excised. She appeared to be recovering, but two days later died of massive multiple pulmonary emboli.

Case 37. A 25 year old woman had had hyperthyroidism for one and one-half years, diagnosed and treated elsewhere. Exophthalmos had first been evident two weeks after the death of her mother, one year before examination here. Prior to our seeing her she had noted diminution of vision for five weeks and a corneal ulcer for five days. Hyperthyroidism had been controlled by the administration of iodine and propylthiouracil for six months, and propylthiouracil without iodine for three months. After the onset of hyperthyroidism she had lost 25 pounds in weight, some of which had been regained.

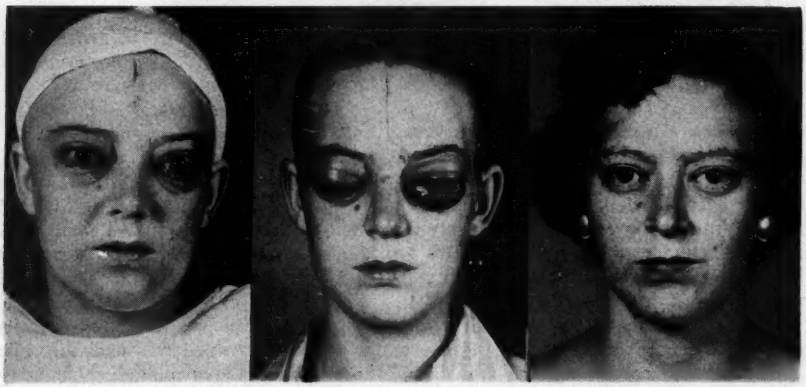
Physical examination revealed a 40-gm. (estimated size) diffuse goiter, a pulse rate of 100 per minute, and the skin changes and the fine tremor characteristic of hyperthyroidism. Her blood pressure was 124/74 mm. Hg. She had severe infiltrative exophthalmos, marked lid retraction, severe multiple extraocular muscle palsies, a left corneal ulcer and proptosis. (The exophthalmometric measurements were 30 and 31 mm., right and left, respectively.)

The results of laboratory tests were normal, including a basal metabolic rate of minus 5%, a 24-hour radioactive iodine uptake of 33%, and blood cholesterol of 230 mg. per 100 ml.

During the first 10 days in the hospital there was a definite increase in chemosis and exophthalmos bilaterally, with further limitation of gaze in all directions. A right frontal craniotomy was performed and the anterior lobe of the pituitary was treated with electrocautery. The stalk was thoroughly treated with cautery where it entered the hypophysis and it was divided. A piece of waxed paper was placed between the divided ends.

An improvement was noted in the chemosis and lid edema five days postoperatively (figure 7). For at least two weeks there was a steady and dramatic improvement in the exophthalmos. Most of the lid swelling and much of the chemosis disappeared and the proptosis lessened. During this time there was no evidence of hyperthyroidism.

Laboratory tests done nine days after operation revealed urinary gonadotropins [18] of less than six mouse units per 24 hours, 17-hydroxycorticoids [19] of 4.7 mg., and 17-ketosteroids [20] of 3.7 mg. per 24 hours; an ACTH test showed a 58% decrease in total circulating eosinophils. Three weeks after pituitary surgery the patient was found to have a urinary tract infection that was successfully treated with sulfa drugs and penicillin. Thirst and polyuria developed about two weeks postoperatively and improved with Pitressin therapy.



A B C

FIG. 7. *Case 37.* A. Photograph of patient showing primary improvement eight days after pituitary stalk section and cauterization. B. Photograph of patient three and one-half weeks after pituitary surgery. Note exacerbation of eye signs equal to that in the preoperative state, associated with recurrence of active hyperthyroidism. C. Photograph of patient two and one-half years postoperatively. Note complete disappearance of all evidence of exophthalmos. Symptom-free on supportive therapy.

One month postoperatively it was noted that there had been a weight loss of 15 pounds. Physical examination revealed a warm, moist skin, and a tachycardia of 110 per minute. At this time a basal metabolic rate was plus 19%, and a 24-hour radioactive iodine uptake was 95%. A most remarkable change had occurred: the patient had had a recurrence of active hyperthyroidism in spite of the pituitary surgery, and during this exacerbation the ocular signs became almost as bad as they had been before the operation (figure 7B). Again it was feared that she might lose one or both eyes, and orbital decompression was contemplated. The hyperthyroidism was controlled with Lugol's solution (for two weeks) and propylthiouracil. During this therapy the basal metabolic rate fell to minus 43% and the proptosis again increased markedly, but without associated periorbital edema.

The patient was maintained on Pitressin and propylthiouracil for the first two months. At this time she had a basal metabolic rate of minus 43% and a 24-hour radioactive iodine uptake of 88%. Because of the continual thirst and polyuria and the high radioactive iodine uptake, both medications were continued.

Signs and symptoms of pituitary failure were pronounced in the five months

after operation. Symptoms included an increased need for rest, nocturia and polyuria without Pitressin, amenorrhea, cold intolerance, dry skin, reduced bodily hair and lack of energy. In addition, severe and bothersome hot flashes appeared which seemed typical of those usually seen during the menopause. Such hot flashes are not normally associated with pituitary failure, yet they occurred here, disappeared when estrogen was given, and reappeared again when it was stopped later. The proptosis was less and the eye swelling showed definite improvement.

Laboratory tests revealed a basal metabolic rate of minus 26%, a 24-hour radioactive iodine uptake of 68%, a blood cholesterol of 269 mg. per 100 ml., urinary gonadotropins of less than 13 mouse units per 24 hours, and a positive Power-Kepler water-excretion test.

The patient was given replacement therapy in the form of Pitressin as required, cyclic stilbestrol, and thyroid, ½ grain daily. The administration of propylthiouracil was continued but the dosage was decreased.

The patient was asymptomatic 10 months after operation. She no longer needed Pitressin, artificial menses were occurring at normal intervals, and her eyes continued to improve. She had lost 15 pounds in weight during the preceding three months. Laboratory tests revealed a basal metabolic rate of minus 23%, blood cholesterol of 243 mg. per 100 ml., and a 38% fall in eosinophils after ACTH. The dosage of propylthiouracil was further reduced, and the dosage of thyroid was increased to 1 gr. daily.

Sixteen months postoperatively her eyes continued to show improvement. Exophthalmometric readings at this time were 25 and 27 mm. for right and left eyes respectively. A basal metabolic rate was minus 24%, and the dosage of thyroid was increased to 1.5 gr. daily.

The patient felt well 21 months postoperatively, except for some increased sleepiness. Weight remained stationary after the initial loss. Axillary and pubic hair were very sparse. Laboratory tests at this time revealed a basal metabolic rate of minus 14%, a 24-hour radioactive iodine uptake of 10%, and 17-hydroxycorticoids of 0.6 and 17-ketosteroids of 2.3 mg. per 24 hours. Stilbestrol therapy was continued. The administration of propylthiouracil was stopped, and because of a misinterpretation of orders the patient discontinued taking thyroid as well.

When she returned five months later she had typical signs and symptoms of myxedema, with a basal metabolic rate of minus 39%, a blood cholesterol of 492 mg. per 100 ml., and a 24-hour radioactive iodine uptake of 50%. Urinary hormone assays were again found to be low—gonadotropins less than 13 mouse units per 24 hours, and 17-hydroxycorticoids, 0.7, and 17-ketosteroids, 2.4 mg. per 24 hours. Her eyes continued to improve. The administration of desiccated thyroid, 1½ grains daily, was resumed, and hydrocortisone, 10 mg. daily, was added to the regimen. After one month, administration of thyroid was stopped for two weeks, and at that time a protein-bound iodine level (PBI) was 5 μg. per 100 ml.

Stilbestrol therapy was discontinued for one month, but had to be started again because the patient developed hot flashes and amenorrhea. A moderate hypochromic anemia occurred that responded to iron therapy.

Two and one-half years after pituitary surgery the patient felt very well and there was no suggestion of residual exophthalmos (figure 7C). Exophthalmometric readings were 24 mm. and 23 mm. for right and left eyes, respectively, compared to 32 mm. in each eye when the exophthalmos had been at its peak. The dosage of desiccated thyroid was increased to 3 gr. daily in an attempt to improve the hypothyroidism further. The basal metabolic rate was minus 25%, and blood cholesterol was 300 mg. per 100 ml. There was a suggestion of a return of the polydipsia and polyuria after hydrocortisone was started.

The findings are summarized in figure 8.

The current therapy consists of desiccated thyroid, 3 gr. daily, cyclic stilbestrol, 1 mg. daily, and hydrocortisone, 10 mg. daily. After this regimen had been followed for three months the basal metabolic rate was minus 15%, serum cholesterol, 284 mg. per 100 ml., and the I^{131} uptake, 4% in 24 hours.

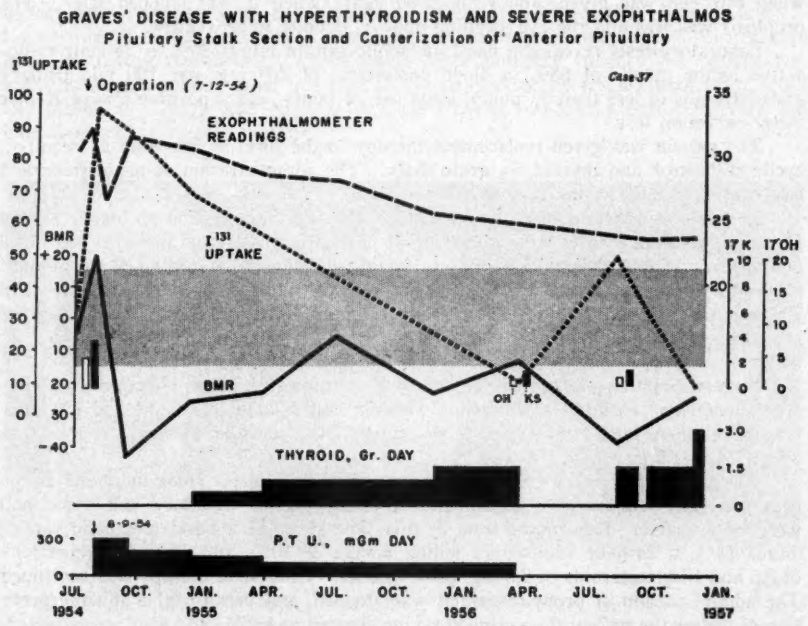


FIG. 8. *Case 37.* Note that the exophthalmos became extremely severe, with marked soft-tissue swelling at the time of the first postoperative rise in basal metabolic rate. Proptosis without visible soft-tissue swelling recurred at the point of extreme fall in basal metabolic rate two months postoperatively.

Comments on Case 37: Some of the most remarkable features of the course of this patient are as follows:

1. The prompt appearance of the exophthalmos following a serious emotional disturbance suggesting a hypothalamic influence.

2. The rapid and marked reduction in infiltrative phenomena within the first two weeks after pituitary cauterization.

3. The reappearance of hyperthyroidism about one month after pituitary surgery, associated with a marked increase in the lid and conjunctival swelling, and a decrease in these manifestations during control of the hyperthyroidism with iodine and propylthiouracil.

4. An exacerbation of the proptosis without increase in infiltrative phenomena during suppression of the basal metabolic rate to minus 43%.

5. Appearance of hot flashes, like those of menopause, which appeared during increasing pituitary failure, were controlled by estrogen and recurred after estrogen was withdrawn. (This appears to us to be of interest.)

6. Occurrence of many features of hypopituitarism, including low levels of urinary follicle-stimulating hormone and steroids, amenorrhea, loss of axillary and pubic hair, and appearance of full-blown myxedema after inadvertent withdrawal of thyroid therapy.

7. Increase of I^{131} uptake from low levels to 50% after the withdrawal of thyroid but in the presence of hypopituitarism and clinical myxedema, which is an unexplained phenomenon. We were disinclined to believe this estimate of I^{131} uptake, but the test was repeated several times with similar results.

8. Gradual and complete disappearance of all evidence of ocular signs of Graves' disease and return of vision to normal. Uncorrected visual acuity had been greatly reduced. It was as low as 20/70 in the right eye and 6/200 in the left eye. Eight months after operation visual acuity was 20/20 in each eye. There was complete recovery of extraocular muscle movements.

The patient is now symptom-free and in good health; she is receiving thyroid, stilbestrol and hydrocortisone.

Case 38. A 41 year old woman developed typical signs of hyperthyroidism and exophthalmos eight months before the date of the pituitary surgery described below. A little later she developed diplopia with associated extraocular muscle palsies, lid retraction and marked lid edema. Exophthalmometric measurements were 25 mm. bilaterally before surgery.

Although she appeared clinically to have mild hyperthyroidism, the results of tests were equivocal. She had lost 11 pounds in weight. On March 5, 1956, the basal metabolic rate was plus 19%; 24-hour I^{131} uptake, 23%; protein-bound iodine, 6 μg. per 100 ml.; serum cholesterol, 140 mg. per 100 ml.

After administration of 4 units of thyroid-stimulating hormone, the 24-hour I^{131} uptake increased to 63%, and this level was not suppressed by thyroid feeding, being 68% after the patient had received 100 μg. of l-tri-iodothyronine daily for ten days, and 77% after 4 gr. of desiccated thyroid daily for 10 days.

Preoperative 24-hour 17-ketosteroid values were 9.4 and 8.1 mg., and 17-hydroxycorticoids were 1.8 and 4.8 mg. per 24 hours. In the four months prior to surgery the exophthalmos had worsened steadily, and the proptosis increased from 24 and 23.5 mm. to 25 mm. bilaterally in spite of 100 μg. of l-tri-iodothyronine daily for 28 days.

On July 5, 1956, a craniotomy was performed, the pituitary stalk was severed, and a plastic diaphragm was placed above the sella turcica. After operation, mild diabetes insipidus developed, and two months postoperatively the result of the Carter-Robbins test was mildly positive.

One week after surgery the periocular swelling had diminished. Exophthalmometric measurements were 24 and 23 mm. in the right and left eyes, respectively. The I^{131} uptake remained relatively high, being 56% in 24 hours, the basal metabolic rate was plus 18%, and protein-bound iodine was 7 μg.

The patient developed some evidences of hypopituitarism. For at least eight months postoperatively she had been known to have amenorrhea. In September, 1956, the vaginal smear resembled that of the castrate, and the endometrium was atrophic.

The urinary gonadotropins measured as follicle-stimulating hormone were less than 13 mouse units per 24 hours on each of two occasions. Repeated serum potassium and sodium measurements were normal. Twenty-four hour urinary 17-ketosteroids were 4.4 and 5.6 mg., and the 17-hydroxycorticoids, 2.2 and 3.0 mg. per 24 hours—not decidedly abnormal, but lower than they had been before operation. The protein-bound iodine levels five and seven months postoperatively were 3 and 2 μg. per 100 ml., respectively, and the basal metabolic rate was plus 5 and plus 6%, respectively. Clinical evidence of hyperthyroidism had disappeared without therapy other than the pituitary surgery.

The severity of the proptosis seven months after operation was only slightly less than that before operation—24 mm. bilaterally as compared to 25 mm. bilaterally. Attention must be called, however, to the fact that before operation there had been a progressive increase in all the associated ocular signs, whereas afterward most of these improved and none increased. In other ways the patient's eyes were decidedly better. There was a marked lessening of lid swelling, and the diplopia which had existed preoperatively had disappeared, although careful muscle testing showed remaining muscle weakness. She could now read newsprint, which she could not do preoperatively.

Comments on Case 38: Among the interesting features of this case are the following:

1. Section of the pituitary stalk and placing of a polyethylene diaphragm above the sella turcica has been followed by measurable but not severe hypopituitarism.

2. The hypopituitarism was manifested by amenorrhea, low urinary follicle-stimulating hormone, atrophic endometrium, and abnormally low protein-bound iodine values; thus gonadotropins and thyrotropin apparently were affected.

3. Clinical evidence of mild hyperthyroidism disappeared, and the basal metabolic rate fell from slightly elevated to normal range.

4. Exophthalmos that had been increasing in severity changed its course. The proptosis decreased slightly, and other signs, including swelling, muscle palsy and visual acuity, improved.

Case 39. A 58 year old man with diabetes mellitus developed exophthalmos with much soft-tissue swelling beginning in October, 1955. About seven months later clinical hyperthyroidism appeared. The thyroid was very slightly enlarged. The basal metabolic rate was then plus 14%; protein-bound iodine, 10 μg. per 100 ml.; I^{131} uptake, 64%. The hyperthyroidism was treated with 4.0 mc. I^{131} in September, 1956. A month later the hyperthyroidism was controlled and the exophthalmos was progressing rapidly. In November pituitary stalk section was performed and a tantalum disc was placed between the severed ends. Orbital decompression or pituitary cauterization was not performed. Therapy included the administration of Lugol's solution, 2 ml. daily for two weeks, propylthiouracil, 400 mg. daily for a few days, and cortisone from the time of operation in doses rapidly diminishing from 200 mg. per day to hydrocortisone, 20 mg. per day. The problem was complicated clinically because the diabetes was erratic and cardiac decompensation was present or impending repeatedly. A left corneal ulcer developed, necessitating enucleation of the eye on December 21, 1956. There has been definite improvement in soft-tissue swelling and vision, but the signs of exophthalmos remain severe. Proptosis has decreased 3 mm. in the right eye six months after pituitary stalk section.

Discussion

The treatment of the exophthalmos of Graves' disease may be chosen today from a fairly varied armamentarium. The measures employed should be chosen with care, chiefly on the basis of the severity or type of ocular changes, and the rate and degree of progression of the disease.

From the present knowledge of the condition, it would seem good practice to try to prevent a tendency to develop exophthalmos whenever possible. When this is attempted, hypothyroidism or hypometabolism should not be allowed to develop in patients having Graves' disease, either before or after therapy for hyperthyroidism. Thus, if exophthalmos is the first evidence of the disease and hypometabolism exists with it, the administration of desiccated thyroid, of thyroxin or of tri-iodothyronine, in at least a physiologic dose, is indicated.

If exophthalmos is increasing in severity, we believe it is advisable to give thyroid hormone in larger than physiologic doses up to the point that can be tolerated by the patient without undue side-effects.

Local measures of treatment should not be overlooked. Cosmetic glasses may be worn. The cornea must be protected from drying and, in cases where the lids close incompletely, ointments may be used during the night or at other times if necessary. Goggles of the type used by "skin divers" are useful. In some cases, tarsorrhaphy may be useful to aid in lid closure or for cosmetic reasons.

The swelling of the periocular tissues is often worse on awakening, and it may be worth while to advise the patient to sleep with the head higher than the body. The prevention of edema by sodium restriction or potassium administration alone has little or no value in this condition.

Roentgen therapy has been recommended by some workers. In general, it has been followed by mild improvement over a period of many months in less than half the patients so treated. How often improvement can be ascribed to treatment is difficult if not impossible to judge. Since hypopituitarism is not caused by a heavy dose of roentgen irradiation, we doubt that the changes are cause-and-effect. It must be admitted, however, that the results of other forms of therapy also are slow to occur and undependable.

Estrogens and androgens as pituitary inhibitors have been of little or no value in the treatment of exophthalmos. Estrogens theoretically may be helpful in preventing the hyperpituitarism associated with the menopause, because ovarian deficiency might aggravate a tendency to produce an excess of hormones other than gonadotropins. If estrogens and androgens are administered, care needs to be exercised that their sodium-retaining power is not adding to a tendency toward edema.

In patients having severe swelling of the lids and conjunctivae, the use of ACTH and cortisone may be valuable. Whether the mechanism of their action involves direct effects upon the local tissue swelling or pituitary suppression, or both, is not known. Even if pronounced improvement follows

the use of these agents, however, experience is not yet sufficient to indicate to what degree or by what measures the improvement can be maintained. It is considered important to limit intake of sodium to 500 mg. per day, and to add several grams of potassium to the daily intake while ACTH and cortisone are being used. If these hormones are administered in large doses, the use of an ulcer regimen also is advisable.

In very severe cases not responding to other measures of treatment, pituitary surgery may be considered. Experience with this type of treatment to date is small but encouraging.

In the event of extremely rapid progression of the disease, when loss of one or both eyes is seriously threatened, orbital decompression may become imperative.

When the condition has become quiescent for a period of many months and ocular muscle palsies are bothersome, eye muscle surgery is useful in some cases.

SUMMARIO IN INTERLINGUA

Es presentate un revista del methodos pro le tractamento de exophthalmo de morbo de Graves, con attention special prestate a observationes relative al effecto de ACTH, cortisona, e—ante toto—chirurgia pituitari. Iodo, estrogenos, e androgenos es considerate como disproviste de valor practic. Quanto al roentgeno-tractamento del glandula pituitari, le autores crede que illo es usualmente de pauc o nulle valor, proque le plus potente doses possibile non ha resultate in le production de mesurabile grados de hypopituitarismo. In certe casos, doses supra-physiologic de thyroide desiccate, de thyroxina, o de l-tri-iodothyronina es administrate meticulosemente. Es citate le resultatos obtenite in 20 patientes per medio de un therapia a l-tri-iodothyronina. In nove de iste casos, un reduction del proptosis ocular de 2 mm o plus occurreva in le curso de periodos de inter duo e 11 menses. Dece patientes esseva tractate con ACTH a hydrocortisona in grande doses. Omnes monstrava melioration symptomatic. Solmente duo monstrava marcate grados de mesurabile meliorationes in lor proptosis. In un de istes, le hyperthyroidismo dispareva intra alicun dies e sin tractamentos de altere forma ha remanite subjugate durante le 10 menses del curso therapeutic in que le doses de hydrocortisona esseva progressivemente reducite.

Chirurgia pituitari esseva empleate in nove casos de severissime o inexorabilemente progressive exophthalmo. Le methodo chirurgic usate in iste casos esseva un de tres typos: (1) Section del stilo solmente; (2) section del stilo e placiamento de un impervie diaphragma super le sella turc; (3) section del stilo e cauterio del lobo anterior del glandula pituitari. Cinque del patientes esseva operate ante le anno 1946. Occurreva melioration del exophthalmo in iste casos, sed a causa del manco de un adequate therapia pro sever hypopituitarismo le operation non esseva usate de novo usque a 1953. Depost ille anno, quatro patientes additional ha essite operate. Un esseva un femina de 64 annos de etate con severissime exophthalmo post-thyroidectomic, hypertension arterial, e grados sever de diabete. Section del stilo e cauterio esseva effectuate, e un rapide e marcate reduction del signos ocular occurreva. Le patiente moriva de embolos pulmonar le vinti-tertie die post le operation. Es reportate le historias de duo altere patientes de maniera plus detaliate. In un de illes, in qui cauterio pituitari esseva executate, il occurreva un rapide reduction del exophthalmo usque a su disparition complete. In le altere, in qui section del stilo esseva

combinate con solmente le placiamento de un diaphragma, le effectuation de hypopituitarismo progredeva plus lentemente. Illo attingeva minus marcate sed definite grados. In iste caso il occurreva un lente sed decidite melioration del exophthalmo in le curso de plure menses.

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JAUNDICE, HYPERLIPEMIA AND HEMOLYTIC ANEMIA: A HERETOFORE UNRECOGNIZED SYNDROME ASSOCIATED WITH ALCOHOLIC FATTY LIVER AND CIRRHOSIS *

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The data to be presented were derived from 20 patients seen at the Minneapolis Veterans Hospital over the last eight years. The symptom complex, findings and predictable course were so strikingly similar one could not escape the conclusion that they comprised a definite syndrome. However, the data were assembled largely retrospectively from records made by physicians unaware of the correlated changes taking place, so they are of necessity incomplete and spotty in individual cases. Nevertheless, in the aggregate the characteristics of the syndrome seem fairly clear.

Sequence of Changes in Individual Patients

The sequence of changes in individual patients best illustrates the characteristic features of the illness following hospitalization. The following five patients are representative of the group, having been selected for completeness of the data. To economize on space and yet allow for comprehensiveness of presentation, the abbreviations and units of various measurements referred to subsequently have been assembled for ready reference in table 1.

Case Reports

Case 1. A 35 year old man who drank beer excessively noticed anorexia, diarrhea, cough, fever, chilliness and right upper abdominal pain seven weeks before admission. The pain lasted approximately two weeks; the other symptoms, however, persisted. He became very weak, and lost 30 pounds in weight. Four weeks after onset of symptoms a physician noted he was intensely jaundiced and gave him "pills" for his fever. However, by the time of admission to this hospital, his jaundice had receded markedly and he felt better. He had had no vomiting, melena, edema or abdominal swelling. In the past he had six or more similar episodes, beginning 11 years previously.

He was slightly icteric on admission and slightly febrile, registering a temperature of 100° F. His blood pressure was 145/85 mm. Hg. His liver descended 5 cm. below the right costal margin on deep inspiration. The tip of the spleen was barely

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TABLE 1

Abbreviations and Units of Various Measurements

A/G	—serum alb./glob., gm. %	MCV	—mean corp. vol., cu μ.
AP	—alkaline p'tase, KA units	Nu RBC	—nucleated red cells
BM	—bone marrow	OsFr	—osmotic fragility
BSP	—bromsulfalein, %	PC	—prothrombin conc., %
BSPc	—corrected BSP, %	Plt	—platelets, thousands/cu. mm.
BT	—bleeding time, min.	RTC	—reticulocytes, %
BUN	—blood urea nitrogen, mg. %	SAm	—serum amylase, u. %
Cbs	—Coombs' test	Sph	—spherocytic red cells
CF	—ceph. flocc., 48 hr.	SR	—sedimentation rate, mm./hr.
CT	—clotting time, min.	StG	—stool guaiac
FBS	—fasting blood sugar, mg. %	TB	—tot. ser. bilirubin, mg. %
FE	—fecal Ehrlich, u./100 gm.	TC	—tot. ser. cholesterol, mg. %
FU*	—fecal urobilinogen, mg./d.	Trsfn	—transfusion
Hb	—hemoglobin, gm. %	TT	—thymol turbidity, units
Ht	—hematocrit, %	UCP	—urine coproporphyrin, μg./d.
Im WBC	—immature wbc	UA	—urine amylase, u./hr.
LB	—liver biopsy	UE	—urine Ehrlich, u./2 hrs.
LE	—"LE" clot test	UU	—urine urobilinogen, mg./d.
Lip	—Lipemia	WBC	—white bl. ct., c./cu. mm./10^3
MCC	—mean corp. hb. conc., %	ZT	—zinc sulfate turb., units

* All values reported in this paper have been corrected for anemia and body weight, taking 15 gm. per 100 ml. as the reference Hb value, and 160 lbs., the approximate average of a large group of normal men, as the reference weight. The calculation was: 15/observed Hb × 160/usual or ideal weight × observed FU = FU corrected for anemia and weight, or indirectly and approximately, for total circulating Hb. FE values were not corrected for anemia.

palpable. Urinalysis was normal except for the presence of bilirubin; VDRL was negative; chest x-ray was normal. Sequential changes in the pertinent laboratory studies are given in table 2. The patient's hemoglobin rose from 9.5 to 15 gm./100 ml. over six weeks, and his reticulocytes reached a peak of 7.9%. The serum cholesterol dropped in six weeks from 656 to 182 mg./100 ml. His jaundice, regurgitation in type, had largely receded by the day of admission, and the serum bilirubin was normal by the third week. The hepatic tests were essentially normal except for slight alterations in the serum proteins and the protein-dependent tests. Liver biopsies obtained during the second and seventh weeks both showed minimal portal cirrhosis (figures 1 A and B).

TABLE 2

Sequential Changes in Various Hematologic and Functional Measurements of Case 1*

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	9.5	2.0	—	2.2	WBC 8.0. SR 85. Ht 37.5. MCV 96. MCC 26.
1	9.8	7.9	656	—	Plt 187. OsFr +. FU 252. 2 StG —. Cbs —. BM: 58% Normoblasts. Foam cells. BSPc 5. CF 1+. TT 8. ZT 8. UU 0.4. A/G 3.7/3.8. PC 70. SAm 112. FBS 75.
2	11.8	7.6	435	1.2	OsFr +. Liver biopsy.
3	14.2	1.9	260	0.7	WBC 14.5 and 6.7. SR 61. Plt 176. FU 98. AP 7. A/G 5.0/2.1. PC 94.
4	13.5	2.9	290	—	WBC 10.0. SR 45. Ht 44. MCV 105. MCC 31.
6	15.2	1.7	182	—	WBC 9.1. SR 5.
7	14.7	1.7	182	—	WBC 10.5. SR 6. BT 4.5, CT 15. BM: 28% Normoblasts. LB.

* Abbreviations and units of measurement in this and the following tables are explained in table 1.

The patient's anemia was macrocytic in type. Two stool guaiac examinations were negative. His fecal urobilinogen excretion was 252 mg. per day despite his having received medicine (probably antibiotics) three weeks previously for his febrile illness. This value falls just at our limit of normal which, for the healthy male of average weight and hemoglobin concentration, is approximately 250 mg. per day. He served as his own control, however, since in the third week his fecal urobilinogen excretion was 98 mg. per day. The osmotic fragility was slightly increased. A screening test was positive during the first week, and the following percentages of hemolysis were observed during the second week:

% NaCl:	.60	.57	.54	.51	.48	.45	.42
Patient, %:	0	3	3	11	24	63	75
Control, %:	0	0	0	1	13	51	64

His Coombs' test was negative.

A bone marrow examination during the first week showed marked erythroid hyperplasia, with 58% of the marrow cells normoblasts. Large phagocytic foam cells (figure 1 C) were relatively abundant. A repeat examination during the seventh week showed only 28% normoblasts and rare foam cells.

X-ray studies of the stomach and gall-bladder were normal. A bone survey, including the skull, pelvis and legs, was negative.

The patient's subjective improvement was rapid, and his enlarged liver receded commensurately. A low grade fever persisted for four weeks. Until the second liver biopsy was obtained he was a perplexing problem to the resident and consulting physicians. The various tentative diagnoses recorded in the chart were: liver disease, type undetermined; hemolytic anemia, cause unknown; and idiopathic hypercholesterolemia. Common duct stone and pancreatitis were considered seriously for a short time after admission, but eliminated because of the rapid, spontaneous improvement and a normal serum amylase. The patient was discharged after 42 days of hospitalization.

Comment: The patient was a puzzling problem of jaundice, anemia and hypercholesterolemia. The first biopsy was considered to be nondiagnostic until it was reviewed with an azocarmine stain at the time of the second biopsy. Hemolysis was suspected but discounted because the alterations were minimal rather than striking. The discovery of foam cells in the bone marrow was a surprising and unexplained finding. The condition improved as the other abnormalities improved. The foam cells probably reflect the previous existence of lipemia. The existence of lipemia was not documented; however, it was not looked for, and the patient had been improving for three weeks before admission. The fact that his first cholesterol was still as high as 656 mg. per 100 ml. after such an interval, in which his jaundice had largely receded, makes one suspect a striking initial hyperlipemia.

Case 2. A 39 year old alcoholic had had anorexia, fever, chilliness and pain in the eyes for 10 days. He had had occasional upper abdominal "gas pains," nausea and vomiting. Four days before admission he noticed jaundice, dark urine and light stools. Two days later all symptoms became worse following excessive brandy drinking; however, he worked until admission.

He was slightly febrile and moderately jaundiced on admission. His liver was palpable 5 cm. below the right costal margin and was tender. His spleen was not

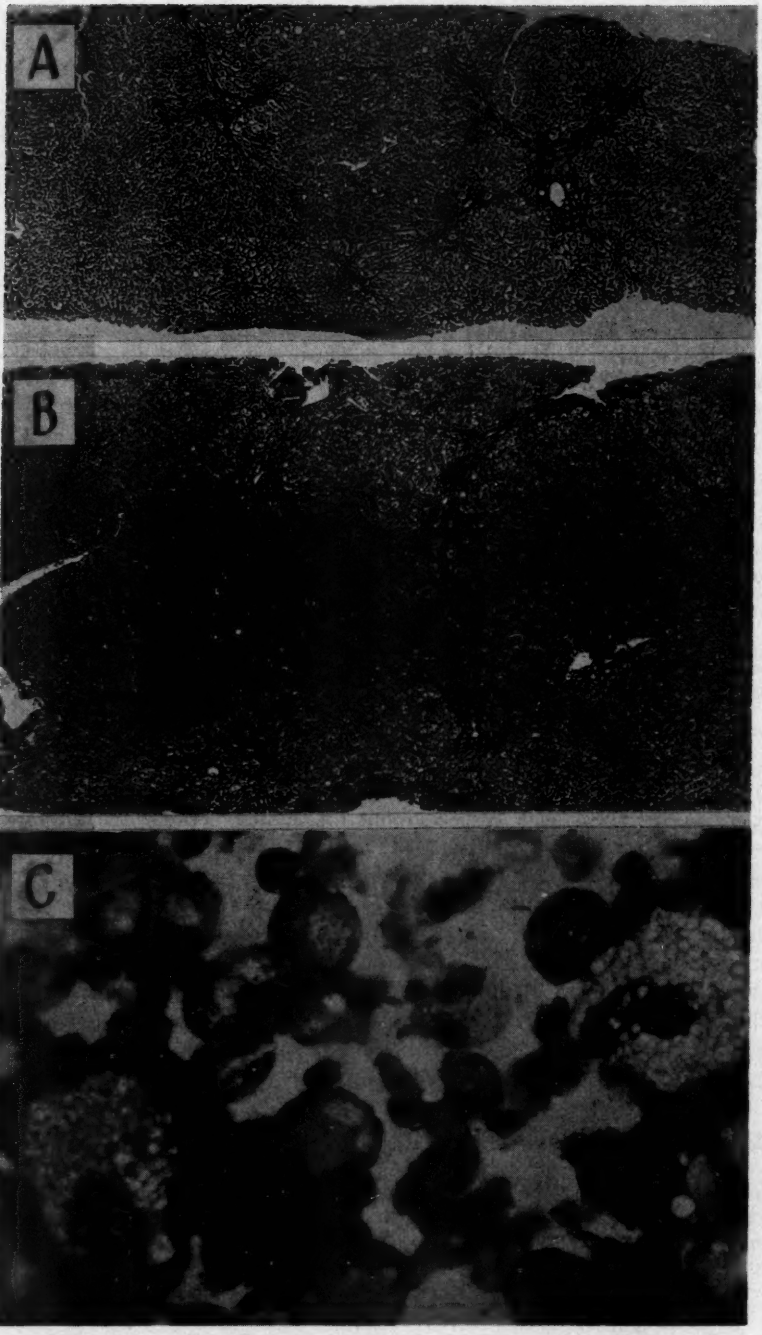

FIG. 1. Liver biopsies, A and B (× 50), and bone marrow aspiration, C (× 400), of case 1.

palpable. His liver receded rapidly, being no longer palpable after one week. His low grade fever, however, persisted for six weeks.

Except for the presence of bilirubin, the patient's urinalysis was negative, as were his VDRL slide test and chest x-ray. The sequential changes in his most pertinent laboratory studies are given in table 3. His hemoglobin remained about 9.5 gm. per 100 ml. until transfusions were given in the fifth week. His maximal reticulocyte response was 7.4%, occurring in the third week. His serum was milky on admission, as noted by the laboratory technician when asked to perform a turbidity test. It cleared rapidly. The serum cholesterol dropped from 536 to 294 mg. per 100 ml. in four weeks. His jaundice was regurgitation in type and improved rapidly, the serum bilirubin decreasing from 9.6 to 1.0 mg. per 100 ml. in four weeks. Hepatic function was mildly disturbed and improved rapidly. His alkaline phosphatase was 68 King-Armstrong units, dropping to 27 by the second week and to 10 by the fourth week.

TABLE 3

Sequential Changes in Various Hematologic and Functional Measurements of Case 2

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	9.6	—	536	9.6	Serum milky. Plt decr. WBC 5.9. SR 29.
1	9.5	5.3	538	5.0	WBC 7.8. SR 75. FE 145. 3 StG —. BSPc 15. CF 0. TT 12. AP 68. UU 2.8. A/G 2.8/3.1. PC 100.
2	9.2	5.9	403	2.2	WBC 7.8. SR 70. Ht 31. MCV 103. MCC 30. Sph. LE —. 3 StG —. A/G 3.9/2.7. AP 27. CF 0. TT 6.
3	8.9	7.4	—	1.6	Sph 1%. Plt 662. Ht 34. FE 121–180. OsFr ±. BM: 64% Normoblasts. UU 0.5. ZT 9.
4	9.5	6.3	294	1.0	FU 276. WBC 14.3. Ht 35. BT 2, CT 10. Trsfn 500 ml. AP 10. TT 4. ZT 11. UU 0.6.
5	16.5	1.6	—	—	Trsfn 1150 ml. Exploration. LB.
7	15.2	0.6	—	0.4	WBC 8.7. SR 6. BSP 3. CF 0. TT 2.

The patient's anemia was macrocytic-normochromic in type. Six stool guaiac examinations were negative. Several random fecal Ehrlich examinations were normal; however, a four-day fecal urobilinogen study during the fourth week was slightly abnormal (276 mg. per day). Spherocytes were seen in the peripheral blood, but an osmotic fragility test was only minimally abnormal. His platelets, which were observed to be decreased in the initial blood smear, rose to 662,000 per cubic millimeter by the third week. An L.E. clot test was negative. A bone marrow examination during the third week showed erythroid hyperplasia with 64% normoblasts.

General improvement was rapid after admission. A gastrointestinal series and cholecystogram were normal. The patient's hematologic findings as well as the initially high cholesterol and alkaline phosphatase values were perplexing to those observing his illness, and diagnoses of hemolytic anemia and common duct obstruction or viral hepatitis were entertained. Following transfusions he was explored surgically during the fifth week, at which time his biliary system was normal, and a liver biopsy was obtained. The biopsy was considered nondiagnostic at the time, so the patient was discharged after 63 days with a diagnosis of hepatitis. However, careful review of the biopsy reveals minimal cirrhosis (figure 2 A).

Comment: The patient presented with hyperlipemia which was unrecognized at the time by all but the laboratory technician. It lasted but a few days. The hypercholesterolemia and jaundice receded over four weeks. During this time the evidences for hemolysis became more marked. The

prominent alkaline phosphatase, together with the hypercholesterolemia in a jaundiced patient, with slight alterations in hepatic function, led to the suspicion of common duct stone and to the surgical exploration in the fifth week.

Case 3. A 46 year old truck driver had been drinking beer excessively for many years. Four years previously he had been explored surgically for abdominal pain and found to have acute pancreatitis. Three weeks prior to this admission he noticed marked tremulousness, weight loss and weakness. Two weeks later he had watery

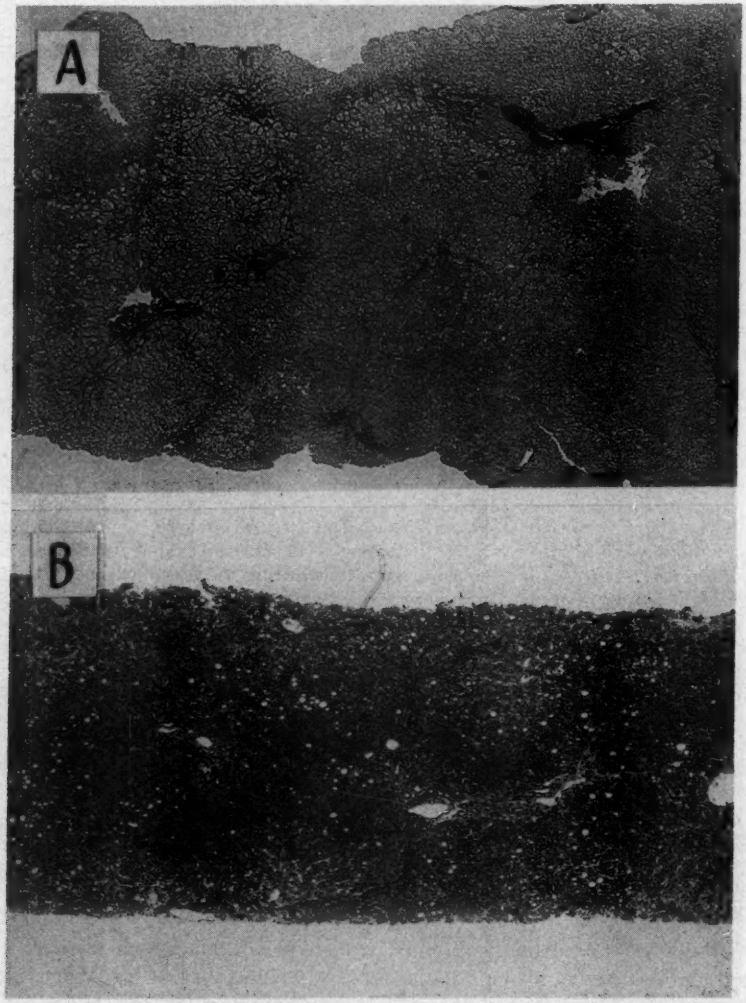

FIG. 2. A. Liver biopsy of case 2 (× 50). B. Liver biopsy of case 3 (× 50).

TABLE 4

Sequential Changes in Various Hematologic and Functional Measurements of Case 3

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	12.5	1.0	—	5.9	Serum v. milky. WBC 8.4. SR 65. Ht 40.
1	11.6	5.3	—	3.6	Nu RBC. Im WBC. FE 159. WBC 10.6. SR 91. A/G 3.3/2.9. SAm 84. FBS 137.
2	11.8	7.6	394	2.5	Nu RBC. Sph. OsFr +. FU 514. Cbs —. BM: 53% Normoblasts. 2 StG —. Plt 303. Ht 37. MCV 104. MCC 32. WBC 10.4. SR 83. BT 2, CT 14. BSP 11. AP 17. CF 0. TT 6. A/G 4.6/2.8. PC 100. BUN 9. SAm 78.
3	11.0	8.8	—	1.6	OsFr +. FE 199. 3 StG —. FBS 107.
4	11.5	6.5	—	1.0	FE 119.
5	12.5	3.8	—	0.7	WBC 12.9. SR 92. FE 213. BT 2, CT 13.
6	13.1	2.6	247	0.5	OsFr +. Plt 324. FU 67. LE —. LB. BSP 11. CF 0. TT 3. A/G 4.4/2.6.
8	12.9	2.0	—	—	
12	13.6	2.9	—	—	OsFr —.

diarrhea lasting several days, and passed several stools containing dark red blood. One week before admission he became jaundiced and noticed epigastric burning and vomiting. On one occasion he vomited a small amount of blood while experiencing a retrosternal burning sensation.

On initial examination he was slightly febrile, markedly tremulous, obese and jaundiced. He had diffuse telangiectasia and erythema of his face and neck, and coughed frequently. His liver was markedly enlarged (16 cm. below the costal margin) and tender. His spleen was not palpable, and was normal in size on x-ray examination. Thrombosed hemorrhoids were apparent on rectal examination, and bloody stool was noted on the examiner's finger. Later, five stool guaiac examinations during the second and third weeks were negative. Except for the presence of bilirubin, his urinalysis was normal. His VDRL slide test and chest x-ray were negative. Sequential changes in his pertinent laboratory findings are given in table 4.

The patient's blood hemoglobin at its lowest was 11 gm. per 100 ml. and improved slowly over many weeks. The maximal reticulocyte response was 10.9%, occurring during the third week, in which the median value recorded was 8.8%. The serum was very lipemic on the day of admission, but cleared over a period of three weeks. This went unnoticed by all but the laboratory technicians. The first cholesterol determination was not obtained until the fourteenth day, at which time it was 394 mg. per 100 ml. By the sixth week it had dropped to 247 mg. per 100 ml. His serum bilirubin decreased from 5.9 (one minute, 3.8) to 0.5 mg. per 100 ml. in six weeks. The hepatic tests were very mildly abnormal or normal. A liver biopsy was not obtained until the thirty-fifth day, at that time showing mild fatty cirrhosis (figure 2 B).

The anemia was macrocytic-normochromic in type. Nucleated red cells, spherocytes and immature white cells were noted in repeated blood smears. Osmotic fragility tests (including one qualitative screening test) on the thirteenth, twenty-first and forty-third days were abnormal (table 5). By the twelfth week the screening test was negative. A Coombs' test was negative, as was an L.E. clot test. His fecal urobilinogen was 514 mg. per day during the second week. In the sixth week this had dropped to 67 mg. per day. A bone marrow examination in the second week showed increased cellularity, with 53% of the cells normoblasts.

X-ray studies of the esophagus, stomach, colon and gall-bladder were normal. The patient's initial fasting blood sugar was abnormal, later decreasing as he improved. He had no family history of diabetes, and a flat plate of the abdomen showed

no calcification in the pancreas. Pancreatitis was strongly suspected initially, but discarded as a diagnosis when serum amylases were normal.

The patient improved symptomatically very rapidly. His liver receded within two months. A low grade fever persisted for six weeks. The hemolytic process was the primary problem that concerned and puzzled his physicians. The mild cirrhosis established by liver biopsy during the sixth week was not considered sufficient to account for the hemolysis, particularly in the absence of splenomegaly. His improvement was progressive, and he was discharged after 55 days of hospitalization with the hemolytic anemia unexplained.

Comment: Though this patient presented with hyperlipemia and jaundice as well as anemia, attention was focused primarily upon the latter. The alterations in his red cells were more pronounced and prolonged than in the preceding two patients, and the evidences of hemolysis more striking. Familial hemolytic anemia was suspected, and various hematologic studies, including osmotic fragility determinations, were made in a brother and in his two children. These were normal.

TABLE 5

Osmotic Fragility Studies in Case 3
(Percentage Hemolysis)

% NaCl	13th day C*	13th day P*	43rd day P*	43rd day C*
.66	0	5	0	0
.60	0	14	2	0
.54	4	54	9	0
.51	9	71	29	6
.48	30	83	74	37
.45	49	91	89	67
.42	74	92	91	90
.36	94	93	94	94

* C, control; P, patient.

Case 4. A 59 year old bartender complained of jaundice, malaise, weakness and fatigue of three weeks' duration. He had noted an intermittent gnawing pain and eructations for two months. The pain was often relieved by food. On admission he was very tremulous and markedly jaundiced, and appeared to have lost much weight. He had a "black" eye. His liver was diffusely enlarged, extending below the level of the umbilicus. The spleen was barely palpable. A few spider nevi were noted. His blood pressure was 154/98 mm. Hg. His initial urinalysis was normal except for the presence of bilirubin. The serologic test for syphilis and chest x-ray were negative.

The sequential changes in the pertinent laboratory findings are recorded in table 6. The patient's hemoglobin at its lowest was 10 gm. per 100 ml., rising slowly. A reticulocyte count of 16.9% was recorded during the second week. His serum was very cloudy on admission, at which time his serum cholesterol was 501 mg. per 100 ml. Five weeks later it had fallen to 208 mg. per 100 ml. During the same interval his serum bilirubin decreased from 20 (one minute of 10) to 1.3 (one minute of 0.7) mg. per 100 ml. His hepatic function was only mildly disturbed. A liver biopsy was not obtained.

The anemia was macrocytic and normochromic. Five stool guaiac examinations were negative. Fecal urobilinogen excretion during the first week was 440 mg. per

TABLE 6

Sequential Changes in Various Hematologic and Functional Measurements of Case 4

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	11.4	—	501	20.0	Serum v. cloudy. WBC 15.1. SR 68. UE 15.
1	10.0	10.0	—	—	Ht 32. MCV 119. MCC 31. BT 15+, CT 9. Plt 198. FU 440. StG —. A/G 3.6/2.6. BSPc 2. CF 2+. TT 9. ZT 11. UU 7.8. PC 47.
2	10.0	16.9	—	—	Sph. WBC 9.3. SR 113. StG —. AP 25. CF 2+. TT 8. PC 48. UE 1. BUN 6.
3	10.9	—	—	4.1	OsFr +. Cbs —. AP 19. A/G 4.2/3.3.
4	12.0	—	—	1.9	3 StG —. BSP 6. AP 13. TT 5. ZT 13.
5	12.1	2.4	208	1.3	OsFr +. Ht 38.5. MCV 100. MCC 32. BSP 10. TT 4. A/G 4.5/2.1.
6	12.4	—	—	—	———
31	14.2	3.1	—	—	———

day. An initial two-hour urine Ehrlich determination showed 15 units, while a repeat study in the second week yielded a value of 1 unit. Spherocytes were observed in the blood smear, and osmotic fragility tests on the fifteenth and thirty-first days were abnormal (table 7), though showing improvement during the interval between tests. The Coombs' test was negative. The bleeding time and clot retraction were abnormal initially; however, no followup studies were recorded.

The patient improved very rapidly after admission. Within two weeks he had a voracious appetite, and his liver had receded greatly. A mild fever persisted for five weeks. X-ray studies of his entire gastrointestinal tract, including the gall-bladder, were normal. The various diagnoses entertained were: infectious hepatitis, portal cirrhosis, obstructive jaundice of intra- or extrahepatic origin, and hemolytic anemia of unknown cause. The latter was the most perplexing aspect of his illness. He was discharged after 45 days of hospitalization.

Comment: The jaundice and the alterations in this patient's red cells were the focus of the evaluating physician's attention. The lipemia would have gone unrecognized except for the comments of the laboratory technician. The bleeding time was prolonged at the time that the platelet count was 198,000 per cubic millimeter. Repeat studies were not made, so we are unable to say how rapidly this abnormality might have cleared up. It was used, however, as a contraindication to liver biopsy.

TABLE 7

Osmotic Fragility Studies in Case 4
(Percentage Hemolysis)

% NaCl	15th day		31st day	
	C*	P*	P*	C*
.66	0	1	0	0
.60	0	8	2	0
.54	0	41	7	0
.51	0	46	22	0
.48	9	90	74	8
.45	73	94	94	62
.42	93	97	97	84
.36	95	97	99	96

* C, control; P, patient.

TABLE 8

Liver Function Test Results Observed in Case 5 at Each Admission

Date		1'B	TB	TC	AP	BSP	CF	TT	UU	Other Tests[10,11]
1–7–49	I	0.1	0.3	193	—	22	0	3	2.7	ZT 8. GT 116. HA 0.79. UCP 432.
4–1–49	I	0.2	0.9	—	—	7	0	—	0.2	SAm 138. LB on 4–7–49.
	F	0.1	0.2	165	—	9	0	4	0.6	ZT 8. GT 27. HA 0.63. UCP 364.
7–18–49	I	0.2	1.0	—	9	6	0	5	—	SAm 48. A/G 5.6/2.3.
11–25–49	I	3.5	5.5	335	—	19c	3+	11	136	ZT 7. GT 42. HA 0.53. UCP 814. SAm 68. FU 249.
	F	0.1	0.5	155	11	—	1+	4	2	A/G 4.7/1.8.
6–21–50	I	10.2	16.2	160	31	32c	3+	10	42	GT 34. HA 0.59. UCP 1091. A/G 3.2/4.5. FU 59.
	F	1.3	2.5	239	14	—	0	5	0.6	ZT 14. A/G 4.0/3.7. LB on 7–1–50.
8–7–51	I	5.7	10.4	332	29	45c	—	25	169	ZT 17.
	F	1.5	3.3	242	20	18c	—	—	—	——
8–26–53	I	10.5	14.5	685	20	13c	0	4	—	ZT 7. FU 320.
	F	0.2	0.5	270	13	15	0	3	—	ZT 7.
6–27–54	I	10.0	17.5	464	39	—	0	14	—	ZT 11. A/G 4.5/2.9.
3–20–55	I	4.6	8.3	548	32	19c	0	4	17	SAm 56. A/G 4.4/3.1.
	F	0.5	1.0	200	10	11	0	5	—	LB on 4–2–55.
6–7–56	I	6.2	9.7	494	44	35c	0	2	2.2	A/G 3.3/2.6.
	F	0.9	1.9	215	24	—	—	—	—	FU 88.

Tests not previously defined: 1'B, One-minute Bilirubin, mg./100 ml. GT, I–V Galactose Tolerance, mg./100 ml. in 60'. HA, I–V Hippuric Acid Excretion, gm./hr. BSPc, bromsulfalein values corrected for presence of jaundice.

I, Initial Studies. F, Final Studies.

Case 5. A 36 year old man was originally called into the hospital on January 7, 1949, during a follow-up study of veterans who had had viral hepatitis during World War II. He had been listed erroneously as having had hepatitis; his service episode was verified by Army hospital records as one of urethritis. He drank excessively and was tremulous at this examination. He was obese, weighing 188 pounds and standing 66 inches. His liver was enlarged. His spleen had been removed 13 years previously for an unexplained rupture. He was not jaundiced, and showed the functional alterations listed in the first line of table 8.

The patient was asked to return for liver biopsy, but did not do so until April 1, 1949, when he became ill following excessive drinking, noting nervousness, chest pain, nausea, vomiting, and tingling and numbness of his hands. His essential physical findings were marked tremulousness and telangiectasia. The liver was not palpable, and he was not jaundiced. He improved very rapidly, and showed the test results recorded in lines two and three of table 8. A liver biopsy obtained on April 7, 1949, showed severe fatty infiltration and possibly minimal portal cirrhosis (figure 3 A).

TABLE 9

Sequential Changes in Various Hematologic and Functional Measurements of Case 5 (Admission of 11-25-49)

Week	Hb	RTC	TC	TB	Other Laboratory Data
1	10.1	13.7	335	5.5	WBC 11.4. SR 37. Ht 36. MCV 102. MCC 31. Nu RBC. Im WBC. FE 308. UU 136. UCP 814. BSPc 19. CF 3+. TT 11. ZT 7. SAm 68.
2	11.7	11.4	—	2.1	Sph. Nu RBC. Im WBC. FU 249. 2 StG —. BM: 50+ % Normoblasts. PC 50. CF 0. TT 5. ZT 8. A/G 4.7/1.8.
3	13.2	5.0	155	1.6	OsFr +. WBC 10.2. SR 17. 2 StG —. UU 10. CF 1+. TT 4. AP 11. PC 72.
4	13.9	0.8	—	0.5	WBC 8.4. SR 17. StG —.
5	14.3	—	—	0.3	UU 2.

On July 18, 1949, the patient was re-admitted with delirium tremens, and the test results listed opposite this date in table 8 were observed.

He continued his excessive drinking, which led to a re-admission on November 25, 1949. At this time he was tremulous, jaundiced and febrile. He had had a cough, chest pain, nausea, vomiting, diarrhea and right upper abdominal pain intermittently for one month. His urine had become dark, and his fingers and toes tingled and were numb. His liver was tender, and was palpable 13 cm. below the right costal margin. Except for the presence of bilirubin his urinalysis was normal. The Kahn test and chest x-ray were negative.

Sequential changes in the pertinent laboratory studies are given in table 9. The patient's hemoglobin rose from 10.1 to 14.3 gm. per 100 ml. in five weeks, and his maximal reticulocyte response was 13.7%. The serum cholesterol was found to be elevated for the first time, and dropped from 335 to 155 mg. per 100 ml. in two weeks. His serum bilirubin similarly decreased rapidly. The hepatic tests were moderately disturbed but improved very rapidly. His urine urobilinogen was disproportionately elevated, probably a reflection of its excessive formation in the presence of a damaged liver, but decreased rapidly.

The patient's anemia was macrocytic-normochromic. Spherocytes, nucleated red cells and immature white cells were seen in the peripheral smear. Five per cent basophils were noted during the second week. An osmotic fragility test obtained during the third week was slightly abnormal, showing the following percentages of hemolysis:

% NaCl:	.57	.54	.51	.48	.45	.42	.36
Patient, %:	0	1	9	18	41	78	96
Control, %:	0	0	0	0	19	45	95

A random fecal Ehrlich determination was 308 units during the first week, and a fecal urobilinogen during the second week was 249 mg. per day. Five stool guaiac examinations were negative. A bone marrow examination during the second week showed erythroid hyperplasia, with over 50% of the cells normoblasts. X-ray studies of his esophagus, stomach and colon were normal. General improvement was very rapid, though a low grade fever persisted for two weeks. All studies improved commensurately, and the patient was discharged after 34 days.

Six months later (June 21, 1950) the patient was re-admitted with delirium tremens and jaundice after continuing his excessive drinking. His liver was enlarged to the iliac crest, and his function was poor, as seen in line seven of table 8. His cholesterol was 160 mg. per 100 ml. initially, and rose to 239 mg. per 100 ml. as he improved, in contrast to his preceding admission. A liver biopsy obtained on July 1, 1950, showed very severe fatty infiltration and moderate cirrhosis (figure 3 B). His fecal urobilinogen during the second week of this admission was only 59 mg. per day. He improved slowly over a period of 37 days and was discharged not yet achieving stabilization.

The patient was next seen one year later (August 7, 1951) with jaundice, epigastric pain, cough, anorexia, nausea and vomiting. He claimed to have abstained from drinking for six months, only to have relapsed following this. However, he had worked only 10 days out of the whole year. He was tremulous, and had a low grade fever, a very large liver and a few spider nevi. His initial and final hepatic studies are given in lines nine and 10 of table 8. Improvement was slow, and he was discharged after a month of hospitalization.

Two years passed before the patient was next hospitalized (August 26, 1953). During this interval he had worked steadily and had abstained from drinking until four months preceding admission, when he again reverted to his previous habits. He developed chest pain, cough, purpura of arms and legs, and jaundice. The liver was very large (palpable 9 cm. below the costal margin).

Sequential changes in the patient's most pertinent laboratory studies are given in table 10. His hemoglobin rose from 10.8 to 14.1 gm. per 100 ml. in seven weeks. Only one reticulocyte count was obtained, the value being 4% in the third week. His cholesterol dropped from 685 to 270 mg. per 100 ml. in four weeks. During the same interval the serum bilirubin decreased from 14.5 to 1.1 mg. per 100 ml. Hepatic function was only mildly disturbed. Unfortunately, a liver biopsy was not obtained at this time.

The patient's anemia was macrocytic and normochromic. He had had no blood loss by history, and one stool guaiac test was negative. Nucleated red cells and immature white cells were seen in the blood smear. The fecal urobilinogen excretion during the third week was 320 mg. per day. A bone marrow examination during the second week showed very marked erythrocytic hyperplasia, with 61% normoblasts and abundant megakaryocytes. Improvement was rapid and progressive, and the patient was discharged after 41 days of continuous hospitalization.

Eight months later (June 27, 1954) he was admitted again with delirium tremens. His drinking habits had changed in that he now drank sporadically and intensely rather than continuously. He was severely jaundiced and had marked hepatomegaly. His function test results are shown in line 13 of table 8. Subjective improvement was rapid, and he was discharged in two weeks when his jaundice was no longer apparent clinically.

Though the patient denied drinking as heavily as previously, he was re-admitted again with mild delirium tremens approximately nine months later (March 20, 1955).

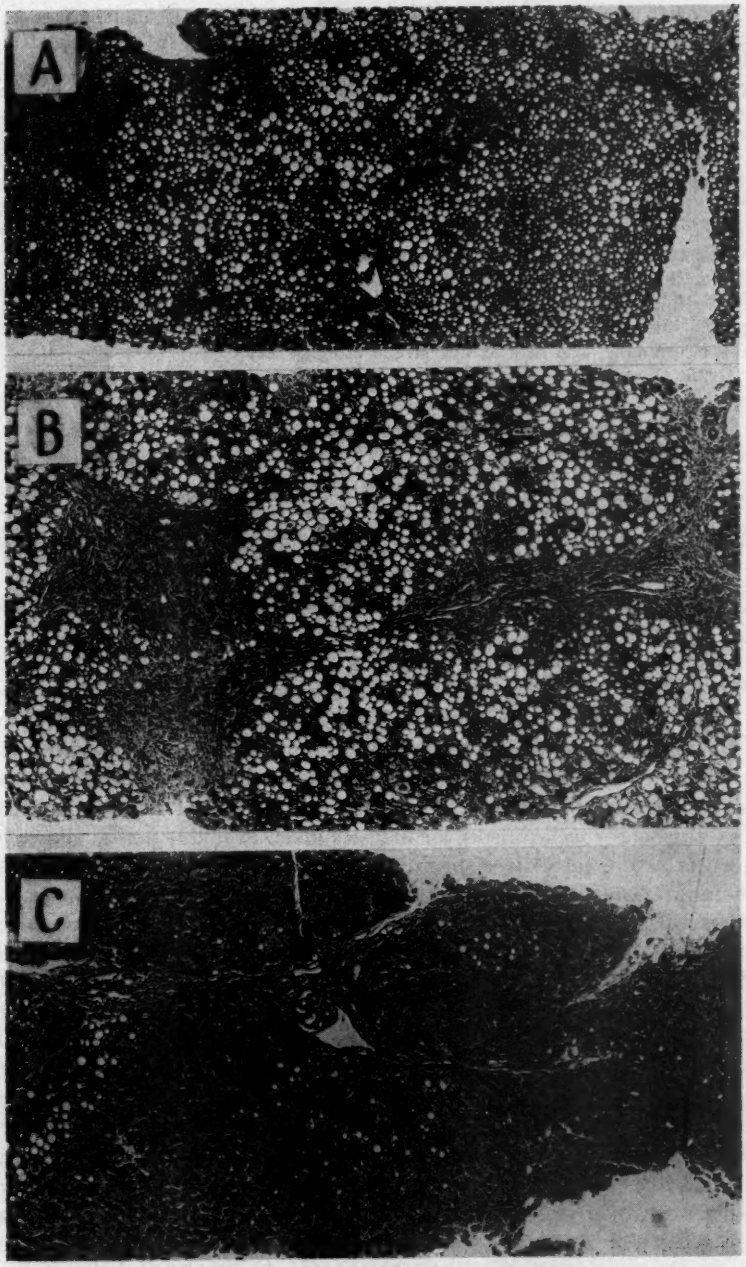

FIG. 3. Liver biopsies in case 5 (× 50). A, 1949. B, 1950. C, 1955.

He was again jaundiced and anemic, and showed rapid, spontaneous improvement in both respects. His initial and final function studies are given in lines 14 and 15 of table 8. A liver biopsy obtained on April 2, 1955, showed mild fatty cirrhosis (figure 3 C). This was greatly improved over the biopsy obtained almost five years previously. Presumably the two-year period of abstinence (1951 to 1953) was beneficial, and his improvement persisted to some extent despite his later relapses.

The last admission (June 7, 1956) was for hematemesis and melena. He had continued to drink, becoming markedly tremulous and finally jaundiced. His function studies are shown in the last two lines of table 8. He required replacement with 4,500 ml. of blood. Fecal urobilinogen excretion two weeks after admission, and after the transfusions, was 88 mg. per day. Esophagoscopy revealed no varices. A gastrointestinal series revealed a questionable lesser curvature ulcer, which was no longer visible on repeat examination one week later. Alcoholic gastritis was strongly suspected but not proved. His response to an ulcer regimen and general hospital care was dramatic, and he was discharged after 34 days.

TABLE 10

Sequential Changes in Various Hematologic and Functional Measurements of Case 5 (Admission of 8-26-53)

Week	Hb	RTC	TC	TB	Other Laboratory Data
0	11.4	—	—	—	Nu RBC. Im WBC. Plt 186. WBC 9.6. SR 82.
1	10.8	—	685	14.5	Ht 39. MCV 118. MCC 28. CF 0. TT 4. ZT 7. PC 68.
2	—	—	—	6.5	BM: 61% Normoblasts.
3	—	4.0	292	—	FU 320. AP 20.
4	—	—	—	2.8	BSPc 13.
5	12.8	—	270	1.1	SR 22. AP 13.
7	14.1	—	—	1.1	SR 12. BSP 17. CF 0. TT 4. ZT 8.
10	14.6	—	—	0.5	SR 5. BSP 15. TT 3. ZT 7. PC 63.

Comments: This patient was seen 10 times over a seven-year period, during which his drinking habits changed successively from severe continuous imbibing to complete abstinence to severe intermittent alcoholism. Three reasonably well-timed liver biopsies taken over this period showed, in sequence, severe fatty liver, probably with minimal cirrhosis; very severe fatty infiltration with moderate portal cirrhosis, and mild fatty cirrhosis. At the time of the first biopsy he was not jaundiced and his serum cholesterol was normal. Seven months later he had his first episode of jaundice, hypercholesterolemia, and probable hemolytic anemia. Seven months after this episode the second biopsy showed severe damage. This time his cholesterol was normal at the height of his jaundice and rose slightly as he improved. Three years later, following a two-year interval of complete abstinence and then relapse, he had another fairly well studied episode of jaundice, hypercholesterolemia and mild hemolytic anemia. Then after an interval of two years he was seen in a similar, incompletely studied episode, at which time the third liver biopsy showed mild cirrhosis. All told, he was seen in six episodes in which jaundice and hypercholesterolemia occurred together and improved rapidly in parallel fashion, and once in association with severe liver abnormality when jaundice was not associated with hypercholesterolemia.

Lipemia was never recorded, but it was never looked for. Only twice was hemolysis thought of and looked for, and in both instances it was dismissed (prematurely, perhaps) as an explanation for the anemia.

Characteristics of the Group

General Clinical Characteristics: The 20 patients were all men aged 26 to 65 years; their average age was 39 years. Alcoholism was uniformly present, though often minimized by the patients. Anorexia, nausea or vomiting, diarrhea and weight loss were common. Malaise, weakness, cough and chilliness were also frequent. Upper abdominal pain was almost always present but varied in severity, at times being very severe. The pain was diffuse or localized to the right upper quadrant or epigastrium. Pancreatitis was frequently suspected initially but not supported by the serum amylase, and so was discounted.

Low grade fever lasting several weeks after admission was the rule. Tremulousness was common, and frank delirium tremens occurred occasionally. Signs suggestive of vitamin B complex deficiency, tongue changes or peripheral neuritis, were sometimes described. Jaundice was uniformly present, though it had often improved greatly by the time of admission. The liver was enlarged, usually markedly, and generally receded rapidly. The spleen was either not palpable or barely palpable; it was never prominent. Edema and ascites were not frequent and, when present, were associated with low serum proteins. Rapid return of serum proteins to normal and loss of retained fluid were typical. An unexplained pleural effusion was observed twice; it was not related to the presence of ascites. Telangiectasia was common, and spider nevi were described occasionally, probably, however, occurring much more frequently than was recorded.

A good appetite was present on admission or became evident within a few days. The patients were often ravenous. Symptomatic and objective improvement was almost invariably rapid, generally surprisingly so.

Liver Function Abnormalities: The maximal abnormalities observed in each patient with various hepatic tests are given in the central portion of table 11, which also lists similar abnormalities in the available hematologic measurements. Though the values recorded in table 11 are the most abnormal ones recorded in the charts of the patients, it must be recognized that they may underestimate the true abnormality that might have been recorded had the test been performed at the optimal time in the course of the patient's illness.

The average maximal abnormality observed with each hepatic test is summarized in table 12, which also lists the week in which the abnormal value occurred. Hepatic function was in general mildly disturbed, though occasionally bromsulfalein retention was marked initially. The more marked functional abnormalities were in general associated with the more severe anatomic alterations on liver biopsy, which are indicated in the next-to-the-

TABLE 11

Maximal Abnormality Observed with Each Measurement in Each Patient

Case	Hb	RTC	TC	TB	Lip	AP	BSP	CF	TT	ZT	A/G	PC	UU	WBC	SR	MCV	MCC	StG	LB*	Miscellaneous
1	9.5	7.9	656	2.2	−	7	5c	1+	8	8	3.7/3.8	70	0.4	14.5	85	105	31	2−	F1+C1+	Sph. OsFr+. FU 252.
2	8.3	7.8	538	9.6	+	68	15c	0	12	11	2.8/3.1	100	2.8	14.3	75	103	30	6−	C1+	Sph. FU 276.
3	11.1	10.9	394	5.9	+	17	11	0	6	u	3.3/2.9	100	u	12.9	92	104	32	5−	F2+C2+	Sph. OsFr+. FU 514.
4	10.0	16.9	501	20.0	+	25	10	2+	11	11	3.6/2.6	47	7.8	15.1	113	119	31	5−	—	Sph. OsFr+. FU 440. UE 15.
5	9.4	13.7	335	5.5	−	11	18c	3+	11	7	4.7/1.8	50	136	11.4	37	102	31	5−	F4+C1+	Sph. OsFr+. FU 249.
6	9.8	11.7	600	14.5	+	31	23c	0	3	u	3.0/2.5	100	u	15.4	102	100	33	10−	—	OsFr±. Clotting defect.
7	10.4	7.2	720	2.3	−	6	7	0	10	11	3.3/2.8	90	u	9.5	86	90	30	3−	F1+C1+	
8	9.8	9.0	520	14.4	+	20	u	0	6	u	3.8/3.3	76	u	15.1	90	101	32	u	—	FE 452. UE 39.
9	11.4	4.8	500	16.8	−	24	40c	2+	14	21	5.4/2.2	100	80	19.1	95	114	31	6−	F4+C3+	FE 300.
10	11.1	8.4	984	1.5	+	34	30c	0	10	8	2.1/1.9	90	u	15.8	106	96	32	1−	F3+C1+	
11	10.1	13.2	250	2.6	−	29	15	1+	4	14	4.6/3.1	94	u	5.1	77	119	32	6−	F1+C2+	Sph. OsFr+. FU 207.
12	11.2	7.8	343	21.0	−	19	17c	0	6	u	4.2/2.7	37	u	13.6	87	u	u	2−	F5+C3+	Nu RBC.
13	11.9	7.0	440	1.4	−	20	7	3+	8	17	4.2/3.9	95	40	14.5	110	u	u	4−	F1+C3+	FE 380.
14	11.7	5.2	354	14.3	−	25	31c	2+	8	u	4.2/2.7	75	1.1	5.0	58	100	31	2−	—	FE 205.
15	12.2	u	584	2.2	+	19	27	0	6	7	4.9/2.2	95	24	11.5	80	91	34	3−	F2+C2+	FU 137.
16	10.8	u	530	43.0	−	25	21c	1+	8	u	3.2/2.6	64	u	6.7	116	u	u	u	F2+C3+	Nu RBC.
17	14.8	u	560	2.2	+	9	26	0	6	16	u	60	u	7.8	20	u	u	u	ND	
18	10.4	4.9	1117	u	+	11	13	0	5	u	u	100	u	7.1	30	u	u	2−	F3+C1+	OsFr+.
19	11.2	8.9	406	8.0	−	26	36c	3+	6	9	2.2/3.5	58	125	11.5	68	117	31	3−	F2+C4+	Sph. OsFr−. FU 204. UA 752.
20	11.0	7.3	361	4.6	+	23	27c	0	5	u	3.2/4.2	100	70	13.6	u	112	34	u	F1+C3+	Sph. OsFr+. FE 449. UA 303.

* F, fatty infiltration. C, cirrhosis. 1+, minimal. 2+, mild. 3+, moderate. 4+, severe. 5+, very severe. ND, nondiagnostic. u, unknown.

last column of table 11. The hepatic tests were as a rule most abnormal during the first or second week following admission, and improved rapidly thereafter.

In addition to the hepatic tests, data on the blood urea nitrogen, serum amylase and fasting blood sugar were available in some patients. The average blood urea nitrogen in 14 patients was 7 mg. per 100 ml., with a range of 3 to 12 mg. per 100 ml. The average serum amylase among six patients was 98 units per 100 ml., with a range of 68 to 144 units per 100 ml. In the last two patients, studied only recently, several urinary amylase studies [7] (normal limit, 300 units per hour) were obtained. In each, abnormal values were observed (752 units per hour in case 19 and 305 units per hour in case 20). Fasting blood sugars were obtained on 11 patients. The values ranged from 65 to 137 mg. per 100 ml., with an average of 92 mg. per 100 ml.

TABLE 12

Maximal Abnormality of Hepatic Tests

Measure	N	Values Observed		Week of Abnormality	
		Average	Range	Average	Range
AP	20	23	7–68	2	1–5
BSP	19	20	5–40	1	1–5
CF	20	1+	0–3+	1	1–4
TT	20	8	3–14	2	1–3
ZT	12	12	7–21	2	1–5
A	18	3.7	2.1–5.4	1	1–3
G		2.9	1.8–4.2		
PC	20	80	37–100	1	1–2

Pathology: Liver biopsies were obtained in 16 of the 20 patients. The results are listed for each patient in table 11. Fatty infiltration was evident in 14, the involvement covering all degrees of severity. Portal cirrhosis was present in 15, being minimal in six, mild in three, moderate in five and severe in one. The one patient with severe cirrhosis had a repeat biopsy within four weeks which showed striking improvement and could no longer be classified as severe. One biopsy was abnormal but nondiagnostic. It was obtained late in a very mildly ill patient.

In addition to those already presented, the following six biopsies (figure 4) illustrate the pathologic changes observed. All of these biopsies were obtained during the second week after hospitalization, though in two instances this was long after improvement had begun.

The first biopsy (figure 4 A) from case 11 shows early portal cirrhosis with minimal residual of fatty infiltration in an azocarmine-stained section. The patient had already improved significantly by admission. He was only slightly jaundiced, and his bromsulfalein retention was 15%.

FIG. 4. Illustrative liver biopsies (× 50) obtained from cases 11 (A), 13 (B), and 18 (C).

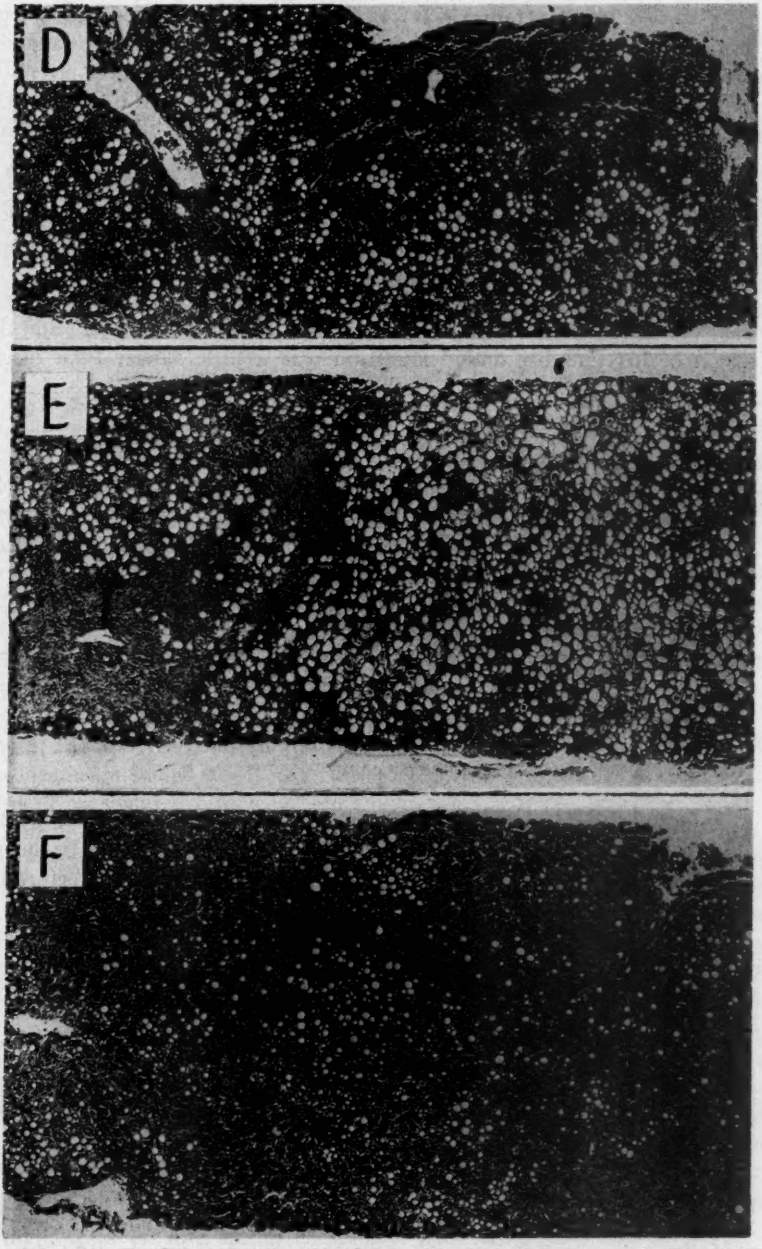

FIG. 4 (continued). Illustrative liver biopsies (× 50) obtained from cases 9 (D), 12 (E), and 10 (F).

The second biopsy (figure 4 B) from case 13 shows moderate portal cirrhosis with minimal residuals of fatty infiltration. This patient's jaundice had receded entirely by the time of admission, and his bromsulfalein retention was 7%. His cholesterol decreased from 440 to 229 mg. per 100 ml. in six weeks, while his bilirubin went from 1.4 to 0.6 mg. per 100 ml. and his cephalin flocculation from 3 plus to zero.

The third biopsy (figure 4 C) from case 18 shows moderate fatty infiltration with the earliest evidences of cirrhosis. The patient's dysfunction was mild; however, his lipemia was intense, the total lipid being 12,106 mg. per 100 ml. In one week it was down to 1,148 mg. per 100 ml.

The fourth biopsy (figure 4 D) from case 9 shows moderate fatty cirrhosis. The hepatic tests of this patient were moderately abnormal, and the recession of his jaundice and dysfunction was a little slower than usual.

TABLE 13

Maximal Abnormality of Hematologic Measurements

Measure	N	Values Observed		Week of Abnormality	
		Average	Range	Average	Range
WBC	20	11.9	5.0–15.4	3	1–5
SR	20	80	20–116	2	1–5
MCV	15	105	90–119	2	1–4
MCC	15	32	30–34	2	1–4

StG − in all patients tested.
OsFr + in 7 of 9 patients.
Plt rise striking in 5 of 6 patients.
FU or FE abnormal or borderline in 9 of 13 patients.
UU or UE disproportionately elevated in 8 of 11 patients.
BM: Over 50% normoblasts in 6 of 8 patients.

His serum bilirubin dropped from 16.8 to 1.4 mg. per 100 ml. in five weeks, while his cholesterol went from 500 to 269 mg. per 100 ml. His hemoglobin dropped after admission from 15.7 to 12.1 gm. per 100 ml. before the biopsy.

The fifth biopsy (figure 4 E) from case 12 shows moderate cirrhosis with very severe fatty changes. The patient's dysfunction was also moderate. His bilirubin on admission was 21 mg. per 100 ml., dropping to 1.3 mg. per 100 ml. in seven weeks.

The last biopsy (figure 4 F) from case 10 shows moderate fatty infiltration with possibly minimal cirrhosis. The patient was only slightly jaundiced and swollen with fluid. His serum was very milky, and proteins were low. His bromsulfalein retention dropped from 30% to 5% in three weeks, during which time his cholesterol went from 984 to 306 mg. per 100 ml., and albumin from 2.1 to 3.7 gm. per 100 ml. His appetite was voracious.

Hematologic Abnormalities: The maximal abnormalities observed with various hematologic measurements are listed for each individual in

table 11 and summarized for the entire group in table 13. The average maximal white count was 11.9 thousand per cubic millimeter; sedimentation rate, 80 mm. per hour; MCV, 105 cubic microns; MCC, 32%. These abnormalities occurred in the second or third week as a rule. Stool guaiac examinations were negative in all patients tested. An average of four stools was examined per patient because of the uniform concern among the ward physicians that the anemia might be due to gastrointestinal bleeding. Osmotic fragility studies were performed in nine patients, in seven of whom the test was abnormal. Platelets were observed to rise strikingly following an initial depression in five of six patients in whom serial values were obtained. Fecal urobilinogen or fecal Ehrlich values were borderline or abnormal in nine of 13 patients in whom valid determinations were made. In only one of the patients were the stool collections made at an optimal time in relation to the course of the illness and the anemia. The values obtained must therefore be taken as minimal estimates of the abnormality actually existing. Urine urobilinogen or urine Ehrlich values were disproportionately elevated initially in eight of 11 patients in whom such determinations were obtained. The values decreased precipitously as the illness improved. The disproportionate abnormality is most likely a reflection of the coexistence of liver dysfunction and increased red cell destruction, since patients with much more liver disease and dysfunction than was shown by these patients do not excrete urobilinogen in such large quantities. Bone marrow studies were obtained in eight patients, six of whom had marked erythroid hyperplasia with over 50% normoblasts.

Abnormalities of Defining Measurements: These are the blood hemoglobin, reticulocyte count, serum cholesterol and serum bilirubin, the four measurements which reflect the essential features of the syndrome. The value of each measure for each individual is given in the first four columns of table 11. The maximal abnormality observed with each of these measures is summarized for the group in table 14. The average maximal hemoglobin abnormality was 10.3 gm. per 100 ml. The lowest hemoglobin was 8.3 gm. per 100 ml. In 11 of 20 patients the hemoglobin decreased after admission by at least 1 gm. per 100 ml. The average decrease was 2.9 gm. per 100 ml. The average maximal reticulocyte count was 9.0%. The average maximal total serum cholesterol was 535 mg. per 100 ml. The highest value observed was 1,117 mg. per 100 ml. The average maximal total serum bilirubin concentration was 10.1 mg. per 100 ml. The highest single value was 43.0 mg. per 100 ml. The jaundice was a regurgitation-type jaundice, the average bilirubin ratio being 57%.

These maximal abnormalities occurred in the first or second week as a rule. Improvement in the jaundice was very rapid, near-normal values being recorded on the average by the third week. Correspondingly, near-normal values for the serum cholesterol and reticulocyte counts were recorded on the average by the sixth week. The response of the anemia was

TABLE 14
Maximal Abnormality of Defining Measurements

Measure	N	Values Observed		Week of Abnormality		Week Values Nearly Normal	
		Average	Range	Average	Range	Average	Range
Hb	20	10.3	8.3–14.8	2	1–4	>5	1–>12
RTC	17	9.0	4.8–16.9	2	1–4	6	4–9
TC	20	535	250–1117	1	1–2	6	2–20
TB	19	10.1	1.4–43.0	1	1–2	3	0–7

Initial serum lipemic in 50%.

variable, the average interval to near-normal hemoglobin values being over five weeks.

The initial serum was lipemic in 50% of the cases. The true incidence of frank lipemia is undoubtedly underestimated, since patients were often not seen at the peak of their illness, and abnormalities of serum lipids were not suspected and so were recognized only inadvertently.

Diagnoses Entertained: The various diagnoses recorded in the charts, either tentatively or finally, are listed in table 15. The diagnosis of portal cirrhosis was generally arrived at following a liver biopsy, being suspected only one-half as often at the initial examination. The variety of diseases included among the tentative diagnoses indicates the confusing aspects of the illness. The elevated cholesterol values in association with some elevation of alkaline phosphatase, slight or absent abnormality of the cephalin flocculation, and the presence of right upper quadrant or epigastric pain and tenderness led to the diagnosis of obstructive jaundice seven times. In one instance a surgical exploration was undertaken despite rapid subsidence of the illness. In the other cases the very rapid evolution and subsidence of the illness precluded surgical intervention and led to a change in diagnosis.

Viral hepatitis was recorded as a diagnosis seven times. In those instances where this was the final diagnosis, it was arrived at by exclusion

TABLE 15
Tentative or Final Diagnoses Recorded

Diagnosis	Times Recorded
Portal cirrhosis	13
Cholangiolitic cirrhosis	2
C.D. obstruction	7
Viral hepatitis	7
Fatty liver	1
Liver disease, c.u.*	4
Acute pancreatitis	4
Anemia, c.u.	4
Hemolytic anemia, c.u.	6
Hyperlipemia or hypercholesterolemia, c.u.	7
Delirium tremens	4
Nephritis	1

* c.u., cause unknown.

rather than on the strength of positive findings. Acute pancreatitis was suspected six times, though recorded prominently as an initial diagnosis only four times. In each instance the diagnosis was discarded because the serum amylase was normal. In the last two patients studied recently, pancreatitis was not suspected clinically, though mild epigastric pain was present. However, urinary amylases were ordered because of a suspicion that these patients in general might have subclinical or atypical pancreatitis with release of enzymes. In both instances the urinary amylase was slightly abnormal.

The anemia was recognized in every patient but one whose hemoglobin was practically normal; however, it was given sufficient consideration to be recorded as one of the diagnoses in only 10 patients. In six of these hemolysis was strongly suspected, though its etiology was invariably perplexing. Hyperlipemia or hypercholesterolemia was recognized as a prominent part of the patient's illness in seven instances; however, its existence was likewise invariably perplexing. Fatty liver, which is probably of preeminent importance in the syndrome, was recorded as a clinical diagnosis only once.

Comment

A rise in serum lipids, including cholesterol, phospholipids and neutral fat, has been recognized in alcoholic fatty liver, though it has usually been considered a slight or at most a moderate abnormality.[8] Documentation of such changes in the published literature has been sparse, and it is not generally appreciated how striking the rise in cholesterol may be, or how frequently frank lipemia will be found if looked for early enough in the course of the illness. In 1918 Feigl [2] made a careful study of the problem, observing some very marked increases in all fractions of the blood lipids in severe acute alcoholism. He noted visible lipemia in one fifth and a rise in blood lipid concentration in two thirds of 30 chronic alcoholics. Lipemia was present in at least one half of my patients, and cholesterol elevation above 500 mg. per 100 ml. was observed in three fifths. These are probably minimal figures, since the observations were usually not made at an optimal time in the course of the patient's illness. Once the patient stops drinking, improvement begins, and proceeds apace. One cannot avoid the delay, usually one to four weeks, due to the patient's failure to seek prompt medical attention. However, one can secure blood for lipid analysis promptly after the initial examination of the patient, and thereby improve on the observations of this report. It is evident from the sequential data of cases 1, 2, 3, 4 and 5 that a delay of only one or two weeks alters the blood findings significantly.

The rise in serum cholesterol, and presumably the other serum lipids, appears to be less extensive the more chronic and the more marked the cirrhotic changes on liver biopsy, and the more severe the dysfunction. Conversely, the more acute the episode and the less evident the cirrhotic changes,

the more intense the lipemia and the more rapid the improvement after hospitalization. This phenomenon is particularly well illustrated by case 5, in whom an episode of jaundice associated with extensive functional as well as anatomic abnormalities (admission of June 21, 1950) was not accompanied by hypercholesterolemia and was slow to improve, whereas one prior and four subsequent episodes associated with milder functional and anatomic alterations were characterized by hypercholesterolemia and rapid improvement.

At present I can only speculate as to the mechanisms involved in the syndrome described herein. The hyperlipemia seems clearly related to an episode of fatty infiltration of the liver. However, one cannot say with assurance whether the lipemia first occurs before or after the beginning of the healing process. Increased mobilization of lipid, whether on the way to or from the liver, is probably the primary etiologic factor. From a consideration of the sequence of serum lipid changes in relation to the clinical histories and physical findings of the patients presented, it seems most likely that the lipemia follows the release of lipid from the fatty liver during the early phase of the healing process.

Another possible etiologic factor is decreased clearing of serum lipids. Two substances of known importance in the clearing action are heparin or a heparin-like compound, and serum albumin. Both could be deficient in these circumstances, and in fact serum albumin was markedly diminished in cases 10 and 19 at the time of its measurement. However, one can hardly consider this a sufficient explanation for the lipemia, since cirrhotics with far more dysfunction and hypoalbuminemia than these patients demonstrated do not show elevated lipids.

Deficiency of nutritional factors very likely contributed to the anemia observed in these patients. However, it seems to me that deficiency alone cannot account for the findings. Hemolytic anemia has been known for a long time [4, 9] to occur in chronic well developed cirrhosis with splenomegaly, though until the recent studies of cell survival [1, 5, 6] it had been considered uncommon. We still do not know its exact incidence, though it is much more frequent than was formerly believed. The hemolytic anemia in these cirrhotics has generally been relatively persistent and associated with prolonged moderate or severe hepatic dysfunction or decompensation. It has not been associated with hyperlipemia or hypercholesterolemia.

The hemolytic anemia in the syndrome of this report is of brief duration, not associated with prominent or persistent hepatic dysfunction, not associated with a prominent spleen, but associated with transient hyperlipemia or hypercholesterolemia. The red blood cells are perhaps altered by an abnormal lipid, becoming fragile. The logical lipid to suspect is lysolecithin. This potent hemolytic agent differs from lecithin, the predominant phospholipid in serum, only in the replacement of one fatty acid by a hydroxyl group. The conversion can be accomplished by pancreatic lipase, which also, in-

cidentally, has a clearing action.[3] Since minute amounts of lysolecithin will affect red cells significantly, one should need only a trace of circulating lipase in the presence of elevated lipids to produce significant hemolysis. Though obvious pancreatitis with amylasemia was not established in these patients, and lipase measurements have not been made under these circumstances, it is tempting to suggest this mechanism in the alcoholic who comes in with fatty liver, hyperlipemia and upper abdominal pain.

Summary

Twenty patients have been observed who exhibited an interesting group of manifestations heretofore not recognized as a distinct syndrome with a predictable course. The essential clinical features are jaundice, hyperlipemia or hypercholesterolemia, and hemolytic anemia. The illness follows excessive drinking, and improves rapidly once the drinking stops, the hyperbilirubinemia and hypercholesterolemia receding over a few weeks. Hemolysis is generally slight and of short duration. The anemia is mild or moderate and does not persist. Hepatic function is usually mildly disturbed and improves rapidly. The anatomic abnormality on liver biopsy is fatty infiltration and minimal to moderate portal cirrhosis.

The patients were generally diagnostic problems until the syndrome was defined. Obstructive jaundice was often suspected initially, and one patient was explored surgically. The anemia was always recognized; however, hemolysis was usually not suspected. Repeated examinations of stools for occult blood were made, with negative findings. In one instance the hemolytic anemia was extensively studied without recognition of the related alterations in blood lipids or in hepatic function. The mechanism of the hemolytic anemia is unknown; however, I suspect that the hemolysis is related to the hyperlipemia, and that an abnormal lipid may be present.

Summario in Interlingua

Esseva observate 20 patientes exhibiente un gruppo interessante de manifestationes que ha non previemente essite recognoscite como un syndrome distincte a curso predicibile. Le aspectos clinic essential es jalnessa, hyperlipemia o hypercholesterolemia, e anemia hemolytic. Le morbo seque excessos alcoholic e se meliora rapidemente si tosto que le uso de alcohol es arrestate. Le hyperbilirubinemia e le hypercholesterolemia recede alora in le curso de alicun septimanas. Le hemolysis es generalmente leve e de breve duration. Le anemia es leve o moderate e non persistente. Le function hepatic es levemente disturbate in le majoritate del casos e se meliora rapidemente. Le anormalitate anatomic trovate in biopsias hepatic consiste de infiltration grasse con leve o moderate grados de cirrhosis portal.

Ante le definition del syndrome, le patientes esseva generalmente problemas diagnostic. Jalnessa obstructive esseva frequentemente suspicite al initio, e in un caso un exploration chirurgic esseva effectuate. Le anemia esseva recognoscite in omne casos, sed le hemolyse remaneva generalmente non suspicite. Repetite examines de feces pro le presentia de sanguine occulte esseva effectuate con constatationes negative. In un caso le anemia hemolytic esseva studiate extensemente sin recognition del re-

lationate alterationes del lipidos del sanguine o del function hepatic. Le mechanismo del anemia hemolytic es incognoscite. Le autor stipula le possibilitate que le hemolyse es relationate al hyperlipemia e que un lipido de natura anormal es presente.

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MUSCLE INVOLVEMENT IN BOECK'S SARCOID *

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Sarcoidosis is a disorder which may affect any part of the body. Most frequently the lymph nodes, liver, spleen, lungs, skin, eyes and the small bones of the hands and feet are involved,[1] but other areas, including the salivary glands, heart, kidney, epididymus, testis, uterus, thyroid, parathyroid, pituitary, the peripheral nerves, brain, meninges and skeletal muscle,[2] may be affected as well.

The concept of sarcoidosis as a disseminated disease is not a recent one. Boeck [3] in 1899 described a patient with skin and lymph node involvement. Cystlike bone radiographic changes in sarcoid were first described in 1902, uveoparotid fever in 1909, and by 1914 the clinical picture of sarcoidosis as we know it was recognized.[2]

Longcope and Freiman,[2] in their review of 160 patients with sarcoidosis, included one with skeletal muscle involvement. Since that time a number of reports [4–16] have described muscle participation in the clinical and pathologic picture of sarcoidosis. Powell [4] reviewed the literature prior to 1953 and found 18 patients with such involvement, the earliest reported in 1919. Nine of these had symptoms and signs referable to the muscle. Seven had palpable muscle nodules, in three associated with stiffness, soreness or weakness, and two others had muscle pain and weakness alone. Powell added six more instances, three of whom had palpable nodules, and in two additional patients noted muscle weakness and atrophy, one so severe as to simulate muscular dystrophy. Maurice and co-workers [5–7] reported seven patients with muscle involvement in sarcoidosis. One demonstrated a clinical picture resembling amyotrophic lateral sclerosis, and a second, a fibrous muscular atrophy. Three of the others had muscle nodules. In a more recent paper, Maurice [8] noted muscle lesions in four of seven autopsied patients with sarcoidosis, and in five of nine patients with sarcoid on muscle biopsy. Lafon and co-workers [9] reported three instances of muscle sarcoidosis, one with localized atrophy, one with a muscle tumor, and one with clinically latent muscle involvement determined by biopsy. Individual patients with muscle sarcoidosis presenting as muscular hypertrophy,[10] contractures,[11] atrophy [12, 13] and diffuse polymyositis [14] have also been reported. Myers et al.[15] described muscle sarcoid granulomata, discovered by random

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biopsy from asymptomatic muscle tissue, in three of four patients with sarcoidosis. His patients were included in Powell's survey.[4] In another study,[16] four of five patients with sarcoidosis but without overt muscle involvement showed granulomata on biopsy of muscle.

It is the purpose of this communication to reëmphasize the participation of skeletal muscle in disseminated sarcoidosis, to consider the frequency of this manifestation and the symptoms and physical findings associated with it, and to evaluate the random muscle biopsy as a diagnostic aid in this disorder.

Materials and Methods

In the 11-year period from 1946 through 1956, random muscle biopsies were done for diagnostic reasons on 42 patients with sarcoidosis at the Presbyterian Hospital of New York. Patients were included in this disease group only if they presented a clinical picture compatible with sarcoidosis and had, in addition, either pathologic proof of the diagnosis (32 patients) or, in the absence of this pathologic evidence, a positive Kveim test (10 patients). The material used for Kveim testing was the same as that reported by Nelson and Schwimmer,[17] and the patients listed here with Kveim tests are included in their study. They found an incidence of false-positive tests of less than 1%.

Table 1 lists the clinical, laboratory and pathologic data on these patients with proved sarcoidosis. It is recognized that the arbitrary delimitation used here might exclude some patients with Boeck's sarcoid but without either pathologic proof or a positive Kveim test. Table 2 includes a group of 25 patients who had some elements of the clinical picture of sarcoidosis and in whom this disorder could not be completely ruled out. These were all the patients with "possible" sarcoidosis on whom muscle biopsies were done in the same 11-year period. These patients have been followed for periods of up to eight years and no further evidence for disseminated sarcoidosis has been found. It is considered unlikely that more than a very few of them have the disease.

Another group of 20 patients is listed in table 3. These were initially considered to have syndromes compatible with sarcoidosis, and muscle biopsies were done during the same 11 years for this reason. Further evaluation demonstrated the presence of other disorders.

None of the biopsy specimens considered here was taken from an area with objective clinical abnormality. They were taken most commonly from the gastrocnemius because of its greater accessibility, although the deltoid, pectoralis major, sternocleidomastoid, platysma and otherwise unidentified neck muscles were also biopsied. The specimens were examined by the Department of Surgical Pathology of Columbia University College of Physicians and Surgeons as part of its normal work load, and in no sense can the results be ascribed to special interest. Three levels were cut routinely

TABLE 1

Muscle Biopsies in Boeck's Sarcoid

Patient	Organs Involved	Muscle or Joint Symptoms	Muscle Biopsy		Other Pathologic Evidence of Sarcoid	Kveim	Calcium, mg., %	Phosphorus mg., %	Alkaline Phosphatase (Bodansky units)	Albumin (Gm.%)	Globulin (Gm.%)	ESR (mm./hr.) (Westergren)	Hand X-ray
			Site	Result*									
1. FR¶	Lung, heart, uveal tract	None	Gastrocnemius	+	None	—	10.6	—	—	3.9	2.5	29	Negative
2. LPe	Lung	None	"Neck"	−	None	Positive	10.4	—	—	4.5	3.2	55	—
3. ML	Uveal tract, parotid, skin	None	Platysma	−	Parotid	—	—	—	—	4.2	4.6	18	Negative
4. KB	Uveal tract, parotid, facial nerve	None	Gastrocnemius	+	None	—	9.6	3.6	3.0	5.0	2.5	9	Negative
5. WJ	Liver, spleen	None	Gastrocnemius	−	Liver	Negative	—	—	20.0	4.0	4.2	90	—
6. CA	Skin (erythema nodosum)	Arthralgia	Gastrocnemius	+	None	Positive	—	—	—	4.0	2.7	116	Negative
7. AL	Hilar nodes, liver	Polyarthritis, muscle pain	Gastrocnemius	+	None	Positive	9.9	3.6	2.6	4.4	2.8	62	Negative
8. GB	Hilar nodes, uveal tract	Polyarthritis	Gastrocnemius	+	None	Positive	10.2	—	—	4.4	3.2	28	—
9. BD	Lung, hilar nodes	Muscle pain	Gastrocnemius	−	None	Positive	11.0	—	—	3.8	2.9	26	—
10. DW	Nodes, meninges	None	Gastrocnemius	−	Lymph node	—	11.0	—	—	4.4	3.6	33	—
11. GG	Hilar nodes, spleen	None	Gastrocnemius	−	None	Positive	10.9	3.9	—	4.4	4.5	24	Negative
12. ET	Lung, skin	None	Gastrocnemius	+	Skin	Positive	9.2	3.0	4.3	4.2	3.4	52	Negative
13. JRo	Uveal tract, liver	Muscle aching	Gastrocnemius	+	None	—	10.1	3.6	—	4.1	3.3	41	—
14. LJ	Meninges, brain	None	Gastrocnemius	−	Meninges, brain (autopsy)	Negative	9.6	4.4	—	4.3	2.3	14	—
15. IT	Uveal tract, facial nerve	None	Gastrocnemius	+	None	Positive	10.3	3.5	3.0	3.5	2.9	20	Negative
16. LR	Lung	None	Gastrocnemius	+	None	—	10.5	3.9	4.6	4.3	2.4	12	Negative
17. GR	Lung, hilar nodes, skin	None	Gastrocnemius	+	None	Positive	9.8	—	—	4.5	3.6	62	Negative
18. RO	Skin (erythema nodosum), hilar nodes	Muscle aching	Gastrocnemius	−	None	Positive	10.1	—	3.5	4.7	2.7	110	—
19. MO	Uveal tract, lung, hilar nodes	Polyarthritis	Gastrocnemius	+	None	—	9.1	—	3.6	3.7	3.3	60	Negative
20. JS	Liver, hilar nodes, skin (erythema nodosum)	None	Gastrocnemius	−	None	Positive	10.2	—	4.2	4.4	3.0	102	—
21. MLo	Liver, spleen, lung	None	Deltoid	+	None	Positive	16.5	4.9	4.6	4.0	2.7	50	Negative
22. AJ	Nodes, liver, spleen, lungs, skin	None	Gastrocnemius	+	None	Positive	12.0	4.5	17.1	4.2	4.6	75	—
23. HB	Hilar nodes, skin, uveal tract	None	Gastrocnemius	−	None	Positive	11.0	4.9	—	3.8	4.6	62	—

TABLE 1—(*Continued*)

Patient	Organs Involved	Muscle or Joint Symptoms	Muscle Biopsy		Other Pathologic Evidence of Sarcoid	Kveim	Calcium, mg., %	Phosphorus mg., %	Alkaline Phosphatase (Bodansky units)	Albumin (Gm.%)	Globulin (Gm.%)	ESR (mm./hr.) (Westergren)	Hand X-ray
			Site	Result*									
24. LL	Nodes, liver, spleen	None	Gastrocnemius	−	Lymph node	—	15.6	—	3.9	3.7	4.7	70	—
25. BC	Uveal tract, nodes, liver	None	Gastrocnemius	+	Lymph node, liver	Negative on steroids	15.3	3.5	22.9	2.8	4.4	90	Negative
26. EW	Uveal tract, facial nerve, hilar nodes	None	Gastrocnemius	+	None	—	—	—	—	4.0	2.5	19	Negative
27. FW	Hilar and generalized nodes, skin	None	"Neck"	+	Lymph node, skin	Positive	9.3	3.1	4.9	3.6	3.5	27	—
28. IW	Nodes, liver	None	Gastrocnemius	+	Lymph node	—	—	—	—	4.3	2.7	—	—
29. RMa	Nodes, lung, parotid	None	Gastrocnemius	+	Lymph node	—	10.3	6.7 (azotemia)	2.7	2.8	3.1	11	Negative
30. FL	Nodes, nasal mucosa, lacrimal gland	None	Deltoid	−	Nasal mucosa	Positive	11.8	4.4	—	2.9	5.6	54	Negative
31. AGr	Hilar nodes, skin (erythema nodosum)	Migratory polyarthritis	Gastrocnemius	+	None	Positive	10.0	—	3.7	3.9	3.3	98	—
32. FF	Cervical and hilar nodes	None	Gastrocnemius	−	Lymph node	—	11.2	—	—	4.3	3.3	11	—
33. EMo	Skin (erythema nodosum), uveal tract	None	Gastrocnemius	−	None	Positive	10.2	—	—	4.5	3.4	61	Negative
34. RD	Parotid, lacrimal gland, uveal tract, nodes	None	Sternocleidomastoid	+	None	Negative	10.0	4.3	3.9	2.5	6.0	36	Negative
35. DJ	Uveal tract, liver, nodes	None	Gastrocnemius	−	None	Positive	10.8	—	3.1	4.5	4.2	48	Negative
36. MJ	Skin	None	Gastrocnemius	−	Skin	Positive	9.6	3.7	4.2	2.9	4.7	25	Negative
37. BP	Skin (erythema nodosum)	Migratory polyarthritis	Gastrocnemius	−	None	Positive	9.1	3.2	—	2.9	3.5	55	—
38. DF	Lung, liver, spleen, nodes	None	Gastrocnemius	+	Lymph node	Positive	11.6	4.0	—	3.9	4.3	77	Negative
39. GA	Node	None	Gastrocnemius	−	Lymph node	—	11.3	3.4	2.0	3.6	3.7	—	—
40. JSu	Hilar nodes	None	Gastrocnemius	−	None	Positive	10.0	3.8	2.2	4.0	3.7	38	—
41. FG	Lung	None	Pectoral	+	Lung	—	—	—	2.9	3.7	3.4	12	Negative
42. WC	Lung, liver, nodes	None	Gastrocnemius	+	Lymph node	—	13.9	3.7	2.5	2.9	3.4	29	Cystic areas in phalanges

* + = sarcoid granuloma present.
− = no sarcoid granuloma present.

in all biopsy material. The sections were stained with hematoxylin and eosin. Special stains were used where necessary. Search for acid-fast bacilli was routinely done when granulomata were seen.

Those biopsies not revealing sarcoid granulomata on original inspection were later resectioned at 10 or more levels in an attempt to determine the true incidence of the presence of sarcoid granulomata.

TABLE 2

Possible but Unproved Cases of Boeck's Sarcoid

Patient	Manifestations	Muscle Biopsy		Kveim
		Site	Result*	
1. DB	Erythema nodosum, uveitis, polyarthralgia	Peroneus longus	—	—
2. PV	Erythema nodosum	Gastrocnemius	—	—
3. AV	Hilar adenopathy	Gastrocnemius	—	—
4. RV	Parotid swelling, conjunctivitis	Gastrocnemius	—	—
5. MH	Chronic pulmonary fibrosis	Gastrocnemius	—	Negative
6. MG	Erythema nodosum and polyarthralgia	Gastrocnemius	—	—
7. WM	Parotid swelling, hepatomegaly	Gastrocnemius	—	Negative
8. MC	Uveitis	Gastrocnemius	—	—
9. TS	Chronic pulmonary fibrosis	Gastrocnemius	—	—
10. RF	Chronic pulmonary infiltration, polyarthralgia, parotid enlargement, peripheral neuritis	Gastrocnemius	—	—
11. CH	Hilar adenopathy	Gastrocnemius	—	—
12. BB	Hepatomegaly, spinal cord disease	Gastrocnemius	—	Negative
13. DP	Chronic pulmonary fibrosis	Gastrocnemius	—	—
14. CR	Chronic pulmonary fibrosis	Gastrocnemius	—	—
15. JT	Chronic pulmonary fibrosis	Gastrocnemius	—	—
16. JM	Chronic pulmonary fibrosis	Gastrocnemius	—	Negative
17. SM	Uveitis	Deltoid	—	Negative
18. EE	Uveitis, chronic pulmonary fibrosis	Gastrocnemius	—	Negative
19. BBa	Chronic pulmonary fibrosis	Gastrocnemius	—	Negative
20. BW	Chronic pulmonary fibrosis	Gastrocnemius	—	—
21. LG	Chronic pulmonary fibrosis	Gastrocnemius	—	Negative
22. FC	Chronic pulmonary fibrosis	Gastrocnemius	—	—
23. AM	Chronic pulmonary fibrosis	Gastrocnemius	—	—
24. AG	Parotid swelling	Gastrocnemius	—	—
25. ES	Erythema nodosum, arthralgia	Gastrocnemius	—	—

* No sarcoid granuloma present.

RESULTS

As can be seen in table 1, 23 of the 42 patients with sarcoidosis showed pathologic changes compatible with that diagnosis on biopsy. Four had sensations of muscle aching or pain. No patient had muscle nodules, atrophy, hypertrophy, contractures or other gross change. Of the four with complaints referable to skeletal muscle, two had granulomata on biopsy and two did not.

Five patients had migratory polyarthritis resembling that of acute rheumatic fever, with no residual joint deformity after the attack, but responding poorly to salicylates. This was associated in two with erythema nodosum.

One of those without erythema nodosum followed his polyarthritis with moderately severe pain in both calves, and is included also in the muscle symptom group. An additional patient had migratory joint pain without heat, redness or swelling, but associated with erythema nodosum. Five of these six patients with joint involvement had muscle biopsies showing sarcoid granulomata. However, 17 patients with sarcoid lesions in muscle had no muscle or joint symptoms whatever.

TABLE 3

Patients Initially Considered as Possible Sarcoidosis

Patient	Final Diagnosis	Muscle Biopsy	
		Site	Result*
1. EM	Ulcerative colitis and ileitis	Gastrocnemius	—
2. JG	Congenital lues with Clutton's joints, uveitis	Deltoid	—
3. BM	Bacterial parotitis	Site ?	—
4. EMa	Pulmonary fibrosis due to tuberculosis	Gastrocnemius	—
5. SJ	Tuberculous adenitis	Latissimus dorsi	—
6. AB	Bronchial asthma, emphysema, pulmonary fibrosis	Gastrocnemius	—
7. JR	Sickle cell disease with parotid swelling	Gastrocnemius	—
8. DK	Lymphosarcoma	Gastrocnemius	—
9. FD	Acute parotitis and conjunctivitis	Gastrocnemius	—
10. VJ	Right middle lobe syndrome due to calcified lymph node	Gastrocnemius	—
11. EL	Bronchial asthma and pneumonia	Gastrocnemius	—
12. LP	Emotional dyspnea	Gastrocnemius	—
13. BF	Probable Hodgkin's disease	Gastrocnemius	—
14. HG	Bronchial asthma and pulmonary fibrosis	Gastrocnemius	—
15. HM	Pulmonary asbestosis and carcinoma	Gastrocnemius	—
16. RM	Primary pulmonary fibrosis (autopsy diagnosis)	Gastrocnemius	—
17. TH	Bronchiectasis, chronic, with emphysema	Gastrocnemius	—
18. JMa	Inactive tuberculosis with pulmonary fibrosis	Gastrocnemius	—
19. HC	Probable Hodgkin's disease	Gastrocnemius	—
20. SS	Pulmonary and lymph node tuberculosis	Gastrocnemius	—

* No sarcoid granuloma present.

Table 1 details the laboratory results of significance in these patients. Twenty-three had had x-rays of the hands taken, 17 with and six without sarcoid granulomata in the muscle. Only one patient showed cystic changes in the phalanges compatible with sarcoidosis: he had sarcoidosis of skeletal muscle.

There was no evidence that the blood calcium or globulin levels or sedimentation rate was related to the presence of sarcoid lesions in muscle. If anything, the serum globulin tended to be higher in the patients without muscle biopsy evidence of the disease. There was no significant difference in the mean calcium or globulin levels, or in the number of patients with elevations of these levels, between the group with muscle sarcoidosis and the group without.

Table 4 shows the relationship between dissemination of sarcoidosis, as measured by the number of organs and tissues involved (other than muscle), and the presence of granulomata in muscle. Of 17 patients in this study with one or two organs involved, only six had a positive muscle biopsy. Seventeen of 25 patients with three or more organs or systems involved revealed muscle granulomata on biopsy.

There was no relation between age, sex or race of the patient and the presence or absence of sarcoid granulomata in the muscle.

Twenty-seven patients were tested with Kveim antigen. Twenty-three of these showed the characteristic sarcoidal response. Two patients with active disease and muscle biopsies showing granulomata had negative Kveim tests while on steroid therapy. Cortisone and ACTH have previously been reported as being able to suppress the development of the Kveim reaction.[18] Another patient with a negative test had his disease limited to his meninges and brain, while sarcoidosis in the fourth patient involved only liver and

TABLE 4

Relation of Organ Involvement in Sarcoidosis to Muscle Involvement

	Muscle Granulomata	No Muscle Granulomata
One organ involved	2	4
Two organs involved	4	7
Three organs involved	12	7
Four or more organs involved	5	1

spleen. The latter two patients had no pathologic evidence of muscle involvement. However, 12 of the 23 patients with positive Kveim tests also did not show sarcoidal lesions on muscle biopsy. To look at the problem in the other direction, except for the two whose Kveim test may have been suppressed by steroid administration, all patients with sarcoid in the muscle who were tested with Kveim antigen showed positive skin tests.

The resectioning of the 19 originally negative muscle biopsies succeeded in discovering one previously unseen sarcoid granuloma (case 40 in table 1). Since this was not found on the original study, he is listed as having had a negative muscle biopsy.

PATHOLOGY

The typical lesion of sarcoidosis (figure 1) found in the muscle was essentially similar to that found in other organs and tissues. It consisted of one or more usually circumscribed nodules, composed chiefly of histiocytes or "epithelioid" cells. Lymphocytic infiltration was present but was usually slight. Giant cells of the Langhans type were usually found but were absent in some sections. Caseous necrosis was never seen, and special studies to demonstrate the presence of tubercle bacilli were invariably negative. The granulomata were most commonly paravascular in location, but were also found within the connective tissue sheath of the muscle. Atrophy

FIG. 1. Multinodular sarcoid granuloma in muscle. Hematoxylin and eosin. × 150.

of muscle fibers adjacent to the granuloma and, less commonly, degenerative changes in nearby fibers were also seen.

The relationship of the sarcoid lesion to small arteries and arterioles requires further consideration. In one of our patients (case 7 in table 1), no typical granuloma was found. However, a small artery surrounded by

epithelioid cells and infiltrated with lymphocytes and polymorphonuclear cells was seen (figure 2). The lumen was partly encroached upon but was not thrombosed, and there was no necrosis of the wall. The finding of a granulomatous arteritis in Boeck's sarcoid is in confirmation of earlier observations.[7, 19, 20, 21] In other lesions, the granuloma impinged upon the adventitia of a small artery or arteriole (figure 3).

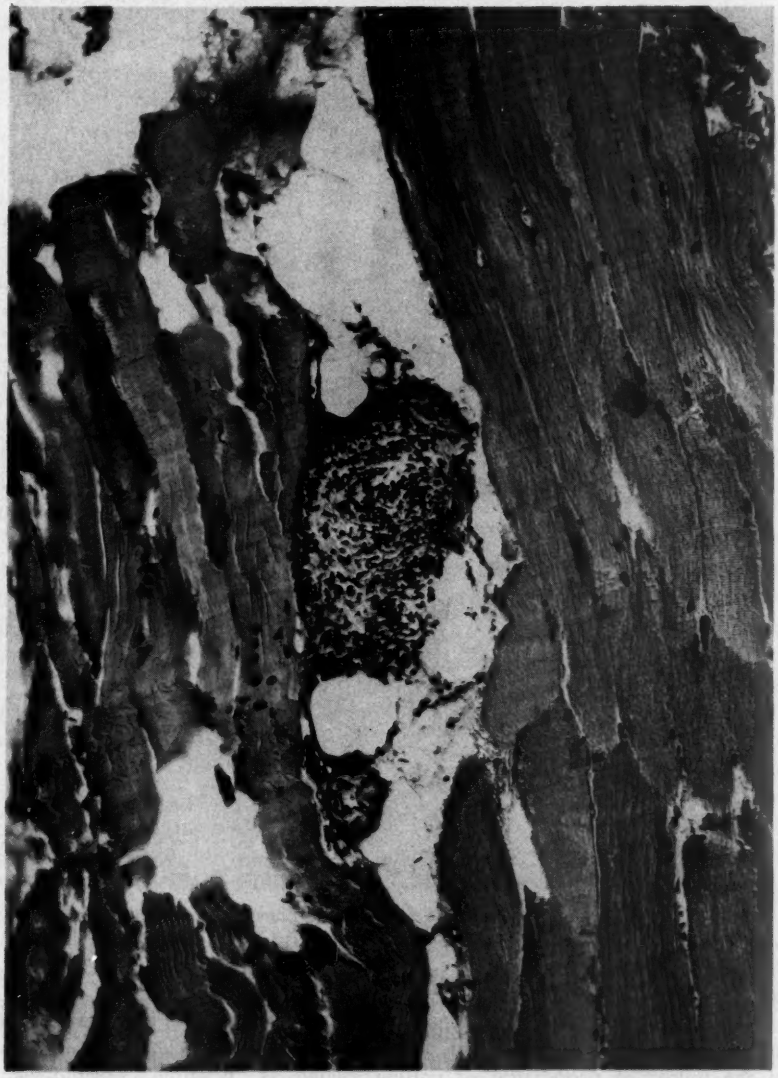

FIG. 2. Granulomatous arteritis due to sarcoid. Hematoxylin and eosin. × 190.

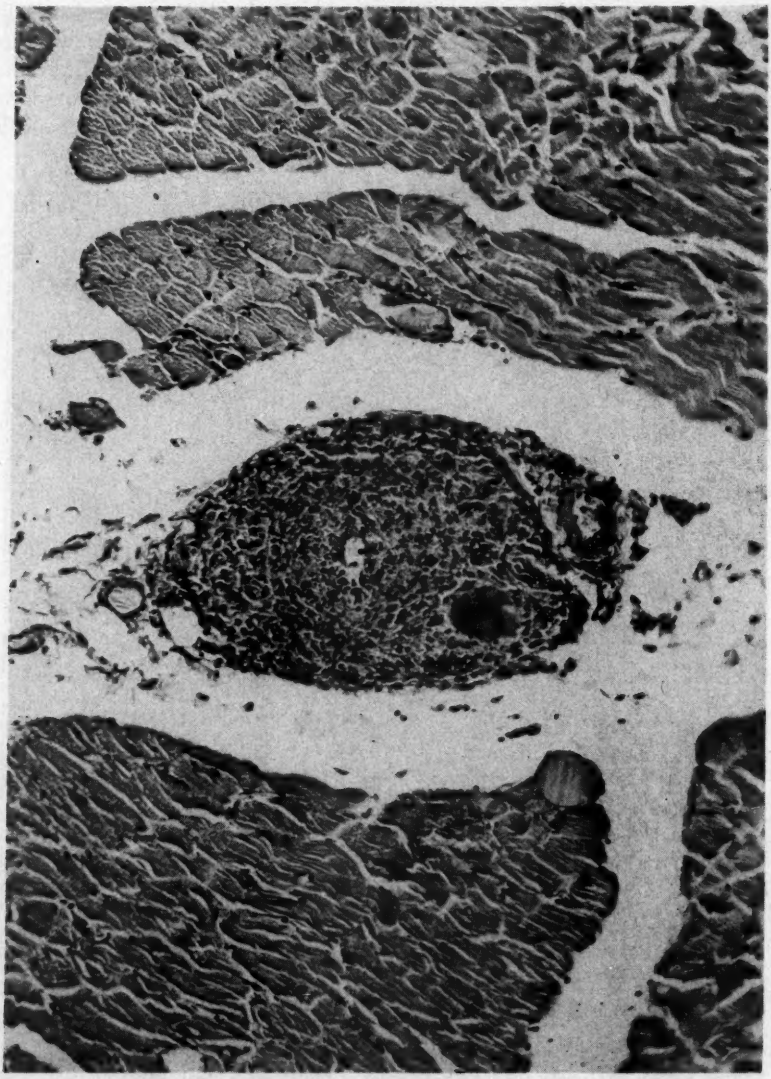

FIG. 3. Sarcoid granuloma in the adventitia of a small artery. Hematoxylin and eosin. × 150.

DISCUSSION

Twenty-three of the 42 patients with proved sarcoidosis had granulomata on random muscle biopsy from objectively normal muscle. The inclusion of the unknown proportion of patients listed as "possible" sarcoidosis in

table 2 who will ultimately prove to have the disease will, of course, lower the percentage of positivity. Nevertheless, the use of the muscle biopsy as a diagnostic procedure in Boeck's sarcoid is indicated, especially in the absence of other available tissue for examination. Eight of our 23 patients with positive muscle biopsies also had accessible tissue elsewhere which on biopsy showed sarcoid lesions. In two of these, lesions were found in the liver and lung on biopsy; both procedures are fraught with greater danger than muscle biopsy. In 15 patients there was no other accessible tissue by which the diagnosis could be established.

The sarcoid granuloma has been shown not to be specific for sarcoidosis. A number of other disorders may produce lesions morphologically very similar to Boeck's sarcoidosis; these include tuberculosis, histoplasmosis, coccidioidomycosis, helminth infection, tuberculoid leprosy and local beryllium, silicon and lipids.[22] None of these, however, has been demonstrated to involve muscle with any frequency, if at all. None of the 42 patients described in this paper had or subsequently developed proved tuberculosis.

This study is part of a wider survey of 552 muscle biopsies done at the Presbyterian Hospital of New York during the period from 1946 through 1956.[23] Other than the 23 with sarcoidosis reported here, only one patient showed granulomata compatible with sarcoid on muscle biopsy. She was a woman with classic scleroderma and with no clinical evidence of sarcoidosis at that time. Shortly after the muscle biopsy she was lost to follow-up. None of the remaining 528 biopsies revealed lesions compatible with sarcoidosis.

One woman, not included in our series, had uveitis. A radical mastectomy was done for carcinoma of the breast. The regional lymph nodes and the pectoralis major muscle showed granulomata compatible with sarcoid. The presence of sarcoid-like lesions in lymph nodes draining neoplastic tissue has previously been reported,[24, 25] but similar granulomata in adjacent muscle have not been described. No random muscle biopsy was done in this patient, and follow-up failed to reveal evidence, other than uveitis, for Boeck's sarcoid.

The muscle lesion of sarcoidosis in our 42 patients was not associated with specific muscle symptoms or signs in the majority. Myers'[15] three patients with asymptomatic sarcoidosis of muscle had polyarthritis, while a fourth with polyarthritis had a negative biopsy. On the other hand, Phillips and Phillips[16] reported four patients with sarcoidosis with positive random muscle biopsy, none with muscle or joint findings.

In our experience, a closer, albeit rough, correlation was possible between the dissemination of the disease and the presence of granulomata in the muscle. The greater the clinical involvement of other organs, the more likely was the muscle biopsy to reveal lesions.

Our experience shows that the sarcoid granuloma when present may be difficult to find in muscle. The total muscle mass of the human adult

represents from 40 to 45% of his body weight,[26] or in the 70-kilogram man, at least 28,000 gm. The average weight of the tissue removed at muscle biopsy is probably 1 gm. or less. It is clear that, to find sarcoid granulomata at all in a random biopsy of the muscle, the lesions must be widely disseminated. Many of our patients with positive muscle biopsies had only

FIG. 4A. Typical sarcoid granuloma.

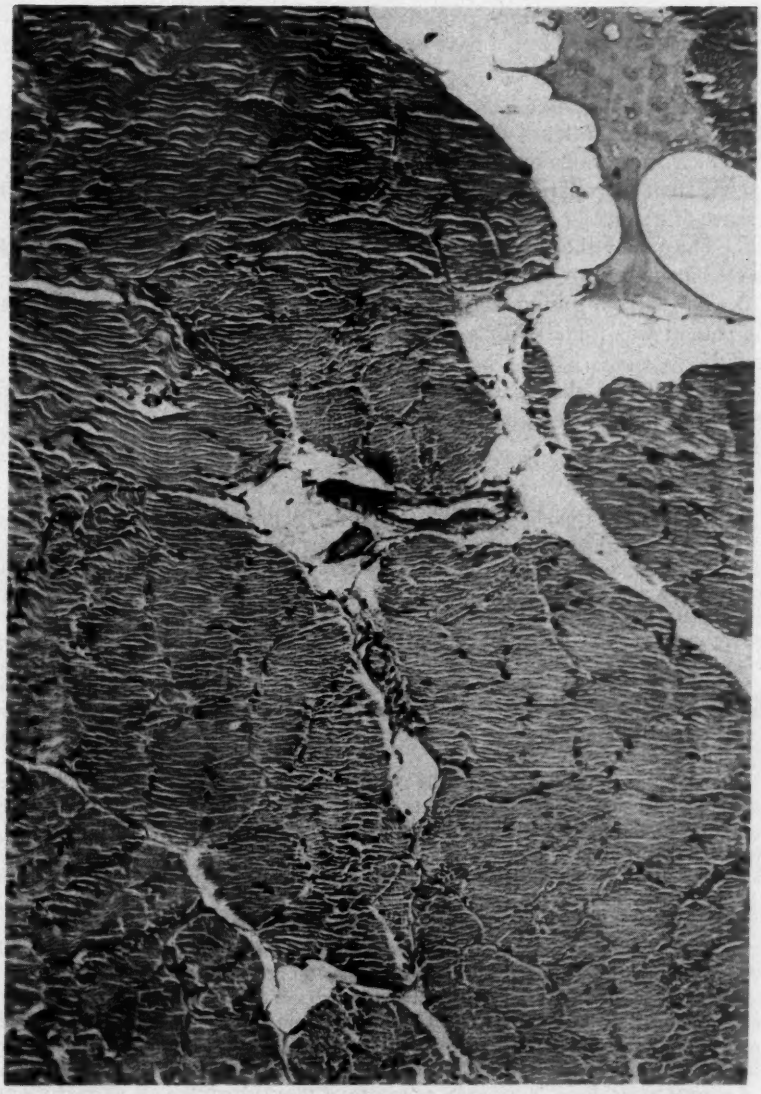

FIG. 4B. At the next level sectioned in the same specimen, no sarcoid tissue is visible. Hematoxylin and eosin. × 150.

one granuloma in the specimen. Routine sectioning at several levels was undoubtedly of great importance in discovering lesions of such infrequency. This is exemplified by figures 4A and B. Figure 4A shows a sarcoid granuloma in muscle. No diagnostic changes were seen at the next level sec-

tioned in this same specimen (figure 4B). If this latter had been the only section obtained, there would have been no pathologic evidence of sarcoidosis.

Conclusions

1. Forty-two patients with proved sarcoidosis are reported, 23 of whom showed sarcoid lesions on random biopsy from skeletal muscle. There was no consistent correlation between objective changes in muscle and the presence of lesions.

2. The wider the dissemination of the sarcoidosis, the more likely the muscle biopsy was to show sarcoid lesions.

3. The sarcoid granuloma in muscle was similar to that in other tissues. One patient was found with a granulomatous arteritis in the muscle due to sarcoid.

4. Because of the sparsity of lesions, routine sectioning at multiple levels proved to be of great importance in discovering sarcoid lesions in muscle.

Summario in Interlingua

In le curso del 11 annos ab 1946 usque al fin de 1956, biopsias muscular con objectivos diagnostic esseva effectuate in 42 patientes con sarcoidosis vidite al Hospital Presbyterian de New York. Nulle patiente esseva includite in iste gruppo qui non presentava—a parte un aspecto clinic compatibile con sarcoidosis—(1) le prova pathologic del diagnose (32 patientes) o (2) in le absentia de un tal prova, un resultato positive in le test de Kveim (10 patientes). Nulle specimen de musculo esseva prendite ab un area con objective anormalitates clinic.

Vinti-tres del 42 patientes con sarcoidosis presentava pathologic alterationes muscular que esseva compatibile con ille diagnose. Vinti-duo monstrava granulomas identic con illos vidite in altere histos in iste disordine. Un habeva un arteritis granulomatose.

In nostre patientes il existeva nulle relation inter le presentia de alterationes sarcoide in le musculo e factores como etate, sexo, racia, symptomas muscular o articular, resultatos del test de Kveim, rapiditate del sedimentation, alterationes radiologic, o nivellos sanguinee de calcium o globulina. Tamen, quanto plus extense esseva le dissemination del sarcoidosis, tanto plus probabile esseva le constatation de lesiones in le musculo.

Es recognoscite que le granuloma sarcoide non es specific pro sarcoidosis. Multe altere morbos produce lesiones que es morphologicamente similissime al lesiones vidite in sarcoidosis. Sed nulle de ille altere lesiones affice le musculo con ulle grado de frequentia (si del toto). In un revista plus extense (de 552 biopsias muscular effectuate a iste institution in le curso del mesme 11 annos), solmente un patiente non-sarcoide exhibiva granulomas muscular compatibile con sarcoidosis. Iste patiente habeva scleroderma classic.

Lesiones sarcoide in le musculo es sparse, e le uso routinari de sectionamento a nivellos multiple se ha provate de valor in lor discoperta. Nonobstante, le uso de biopsia muscular como technica diagnostic in sarcoide de Boeck es indicate, specialmente quando nulle altere specimens histologic es disponibile pro le examine.

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THROMBOTIC THROMBOCYTOPENIC PURPURA: A REVIEW OF THE LITERATURE WITH REPORT OF A CASE*

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Thrombotic thrombocytopenic purpura has become recognized as a clinical entity only in recent years. This uniformly fatal disease, which may affect either sex at any age, is characterized by the clinical triad of hemolytic anemia, thrombocytopenic purpura and varied central nervous system abnormalities. The pathologic picture primarily shows changes in the arterioles, with the formation of poorly understood hyaline thrombi.

It is the purpose of this paper to review the available literature on this subject and to add a case report. This disease was thoroughly reviewed by Barondess [1] in 1952, but further reported cases have helped to increase our knowledge of this still inexplicable illness.

Thrombotic thrombocytopenic purpura was first described by Moschcowitz [2] in 1925. His case was of a 16 year old girl who developed weakness of the arms, and pain on motion of the wrists and elbows. By the time of her admission to the hospital 10 days later a few petechiae and marked pallor were noted. She lived 17 days from the onset of her illness. Before death she developed high fever and hemiparesis, leading to pulmonary edema and coma. Autopsy showed numerous thrombus-like lesions in the terminal arterioles and capillaries. The lesions were fairly widespread, but were seen primarily in the heart and kidneys. Moschcowitz recognized the hemolytic nature of the process. He felt that death "—resulted from some powerful poison which had both agglutinative and hemolytic properties."

Baehr, Klemperer and Schifrin [3] reported four cases in 1936, all in females, ranging in age from nine to 48 years. One case had mild transient urticaria one month preceding her illness, while another had an antecedent upper respiratory infection. This same patient had had mild arthritis for one year. The disease was rapidly fatal in all four cases. Fever, purpura and progressive anemia in spite of repeated blood transfusions were noted. Reticulocytosis and normoblasts were seen in the peripheral blood, while the blood indices were normal. The bone marrow showed some increased cellularity of the red cell series. All cases showed mental and neurologic changes, which were variable but gradually grew more severe as the disease process advanced. Autopsy studies showed lesions throughout all organs examined. The authors described the lesions as being granular thrombi with varying degrees of swelling, proliferation and organization of adjacent

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endothelium. The lesions did not stain for hemoglobin, iron or amyloid, while fibrin stains showed little evidence of fibrin. The authors felt that, due to the damage to the capillaries, there followed an extravasation of red blood corpuscles into the tissues, where they were destroyed. It was their opinion that the formation of a thrombus was the primary lesion, and that, secondarily, the endothelial damage occurred. They felt that, due to the many thrombi forming in the tissues, the supply of platelets became exhausted in spite of normal production in the bone marrow.

The next case, reported by Altschule [4] in 1942, was also in a woman. This 50 year old patient had a rapidly fatal course and showed the now familiar manifestations of severe anemia, thrombocytopenic purpura and varied neurologic changes. Altschule felt that the disease should not be classified as being similar to disseminated lupus erythematosus, as had been propounded by Gitlow and Goldmark [5] in 1939. The latter authors had reviewed a case described by Baehr et al.,[3] and felt that the glomerular lesions were compatible with the diagnosis of disseminated lupus erythematosus. Altschule emphasized the differences in the clinical findings of these two diseases and the distinct arteriolar lesions noted in thrombotic thrombocytopenic purpura. He was the first author to propose the theory that endothelial damage was the primary lesion, with the formation of a platelet thrombus a later event.

In 1943 Bernheim [6] reported a fulminating case ending in death within two weeks in a 33 year old woman. This patient had received radiotherapy to an area of adhesive tape dermatitis which had developed two weeks before the onset of weakness and headache. Laboratory studies revealed a slight increase in the cellularity of the bone marrow, hemolytic anemia and reduced platelets. The autopsy revealed the typical capillary and arteriolar lesions. These lesions were noted in the brain for the first time. Areas of ischemic necrosis were noted which the author believed were related to the partial occlusion of the involved vessels. Bernheim felt that the endothelial changes were secondary to the formation of platelet thrombi.

In 1946 Trobaugh, Markowitz, Davidson and Crowley [7] described a case in a 24 year old man whose death occurred within 15 days of the onset of symptoms. His illness was preceded by an upper respiratory infection. The authors felt that the thrombi were composed of platelets. They agreed with Altschule [4] that the vascular damage was primary. They noted that the capillaries in areas of damage showed prominent endothelial cells with vesicular nuclei. This phenomenon was seen in vessels in which no thrombi were present. Bone marrow studies revealed that the megakarocytes had dark, pyknotic nuclei, without any decrease in the total number of megakaryocytes. Many vascular lesions were seen in the bone marrow sections. The authors suggested that icterus was on a hemolytic basis.

The following year Carter [8] reported a rapidly fatal case in a 66 year old Negro. This man developed neurologic changes at the onset of his illness.

In spite of a severe normocytic anemia and a decreased number of platelets, he never developed any clinical manifestations of purpura. The author noted that an occasional arteriole showed slight endothelial swelling as its only evidence of pathology. The typical lesions of the disease were found to be widespread. The author felt that the thrombi were formed primarily by platelets. He could not demonstrate red blood corpuscles, leukocytes or bacteria in the occlusions. In several of the typical lesions he noted marked fibrinoid degeneration and actual necrosis, with extrusion of the thrombotic material into the adjacent tissue. He reiterated the statement of Altschule that the syndrome is not related to disseminated lupus erythematosus, and also added polyarteritis nodosa, "or any of the other diseases of the erythema group." Due to the fact that the lesions were widespread, Carter first suggested the use of biopsy as an aid in diagnosis.

Singer, Bornstein and Wile [9] reported a case in an 11 year old girl, who died five weeks after the onset of weakness, anorexia and fever. A female sibling of this patient died one year later of disseminated lupus erythematosus. Their case was preceded by an upper respiratory infection. In their excellent discussion they felt that the anemia was primarily hemolytic in nature due to some unknown mechanism. They suggested the search for incomplete immune bodies attached to the red blood corpuscles via an antihuman globulin serum. They also advised study of differential fragility tests and liver function tests, as well as assays of splenic "hormone" and quantitative study of the megakaryocytes. It is interesting to note that, on autopsy, in addition to the usual findings, two subdural hematomas were found, a condition not ordinarily seen in thrombotic thrombocytopenic purpura.

In 1947 Fitzgerald, Auerbach and Frame [10] reported three cases, all of a fulminating nature. One patient gave a history of urticaria, sulfonamide sensitivity and rheumatic fever, while another had had rheumatic fever and a history of sulfonamide ingestion one year and also three weeks before the onset of her illness. The authors felt that the possible role of hypersensitivity, such as is seen in the production of periarteritis nodosa, must be seriously considered. Lesions were noted in the bone marrow sections of all three cases. Examination of the skin in one case revealed no lesions.

Engel, Scheinker and Humphrey [11] in 1947 reported a case in a 15 year old Negro girl whose illness was preceded by an upper respiratory infection. She died in three months after having undergone a partial, apparently spontaneous remission. Splenectomy late in her illness was without avail.

In 1948 Muirhead, Crass and Hill [12] described a rapidly progressing case in a 14 year old white girl. Spherocytosis was noted, along with increased red blood cell fragility, both seen only occasionally in the disease. Proliferative glomerulitis, in addition to the usual lesions, was noted. Endothelial proliferation was seen in the absence of local thromboses. The author felt that an unknown type of antigen-antibody response might explain the findings in thrombotic thrombocytopenic purpura.

Epstein, Deschamps and Chiffelle [13] in 1948 reported the disease in a 20 year old woman who died within two weeks of the onset of lassitude, anorexia and weakness. Treatment consisted of multiple transfusions, vitamins, liver extract, Rutin and penicillin. At autopsy a 190 c.c. pericardial effusion was found. The vascular lesions were most prominent in the heart, brain and pancreas. They noted infarcts which were often associated with the occlusive process. The authors believed that the multiple occlusion of small blood vessels is probably responsible for hemorrhages," apparently by a process of diapedesis. Since the lesions were found only rarely in the kidney and lung, they felt it quite unlikely that the disease was embolic. They suggested the use of heparin to inhibit platelet agglutination, but emphasized the potential dangers of attempting such therapy.

Ehrich and Seifter [14] in 1949 reported the seventeenth case in the literature. They described a 24 year old Negro woman who had been taking a medication containing iodine a year earlier and also three weeks before the onset of her illness, which terminated fatally in five days. It is interesting to note that a bone marrow study revealed one lesion of the disease. This patient showed glycosuria and partial necrosis of the islets of Langerhans. The authors postulated that the iodine caused an antigen-antibody reaction on the thrombocytes or megakaryocytes. In turn, they felt that the involved cells agglutinated or disintegrated, causing the capillary occlusions, with a resultant thrombocytopenia with its purpuric manifestations.

During the same year Green and Rosenthal [15] reported three cases. One of their patients had been vaccinated for smallpox three weeks prior to her admission. Electroencephalographic changes were noted to suggest a neoplasm. The patient had variable neurologic clinical findings and extensive vascular lesions of the brain on autopsy. Another patient showed, in addition to the usual pathology, changes indicative of acute pericarditis and myocarditis, plus glomerular alterations in the kidneys, with occasional obliteration of capsular spaces and fusion of tufts. The brain lesions were noted primarily in the cerebral cortex, with very few associated parenchymatous changes being seen.

In 1949 Pagel,[16] in a discussion of acronecrosis due to fibrin thrombi, described the finding of endothelial cell thrombi in five cases, one of which undoubtedly represented thrombotic thrombocytopenic purpura in a 74 year old woman. This patient died within five weeks of the onset of generalized weakness, followed later by purpura, icterus, anemia and coma. Lesions were widespread, except that none was found in the skin or brain. A small hemorrhage was seen in the cerebellum. The other four cases were descriptions of similar lesions seen peripherally in subacute bacterial endocarditis and tuberculous septicemia. He felt that the lesions seen in these two latter diseases were not embolic but due to a generalized endothelial cell proliferation. Pagel felt the vascular changes may be "due to a hypergic response to antigenic stimuli."

In 1950 Gore [17] reported and discussed five cases compiled from the Armed Forces Institute of Pathology. Two of these cases showed no purpura, while in three the prodromal symptoms were prolonged. One patient had had exposure to lead, while another had had a recent upper respiratory infection. Associated diseases noted included sicklemia, subacute glomerulonephritis and extensive tuberculosis. Autopsy findings in all revealed the characteristic vascular lesions. Gore demonstrated focal lesions of arterioles and capillaries,"—upon which platelet thrombi formed and from whence they grew along the length of the vessel." He termed these lesions "prethrombotic," and postulated that the swelling lesions progressed until the overlying endothelium ruptured, over which platelets accumulated rapidly. Although Gore felt that this disease is distinctively different from disseminated lupus, he did not believe a hypersensitivity reaction could be eliminated as an etiologic possibility.

In 1950 Wyatt and Lee [18] reported a rapidly fatal case in a 50 year old white man whose first symptoms were vertigo and mental confusion, with no antecedent history of illness. Although purpura, fever and pallor were present, the outstanding clinical feature was the changing mental pattern, which finally progressed to deep coma. Although choked discs were found, the spinal fluid was clear and under only moderately increased pressure. The total protein was 94 mg.% and the cell count was five. The authors felt that the platelet deficiency was caused by actual depletion of the thrombocytes, with resultant development of the bleeding tendency. They felt this meant postulating primary endothelial damage which might be due to a form of vascular idiosyncrasy. Focal necrosis of the liver and adrenals was seen, in addition to an acute proliferative glomerular nephritis.

Goldenberg, Thayer and Hastings [19] during the same year reported a case in a 23 year old white woman who was admitted to a psychiatric hospital for treatment of a mental depression. Her first symptomatology was headache, followed by a feeling of generalized numbness. Because of developing abnormal behavior, she was hospitalized five days after developing profuse vaginal hemorrhage without evidence of purpura. Blood count revealed a severe anemia, while an electrocardiogram showed ischemic changes. Following the development of petechiae six days later she was admitted to a general hospital. Her course was rapidly downhill. Widespread lesions were found on autopsy. The authors felt the neurologic findings were due to multiple platelet thrombi in the brain. Although the posterior lobe of the pituitary was involved, no lesions were seen in the anterior lobe.

In 1950 Rotter and Altschule [20] reported a case of thrombotic thrombocytopenic purpura in a 23 year old white woman. The patient had had a generalized ulcerative skin lesion which started two months before her death. She was given sulfonamides for a urinary infection one month later. Approximately three weeks following this therapy she developed bleeding from

the mouth, and then purpura, hemolytic anemia resulting in her death five days later. Lesions were found in her heart, liver, adrenals and kidneys.

In 1950 Singer, Motulsky and Shanberge [21] reported an exhaustive hematologic study of a case in a 25 year old white woman. Virologic studies were negative except for a lymphocytic choriomeningitis complement fixation titer of 1:25. An electro-encephalogram was taken after the patient had developed a right hemiparesis. The tracing was consistent with the diagnosis of a diffuse cortical disorder. Aureomycin was employed, without visible effect. Autopsy revealed extensive lesions in all major organs. Occasionally a subintimal accumulation of an amorphous eosinophilic material was seen associated with an endothelial proliferation. They felt the thrombi consisted of platelets.

Red blood cell fragility was thoroughly studied with a variety of methods, including hypotonic saline, lysolecithin, heat and mechanical. All were essentially normal except for an increased mechanical fragility of about twice normal. Coombs' antiglobulin test was negative on three occasions. They concluded that the hemolytic mechanism was not associated with globulin antibodies. Two sternal aspirations and one biopsy with the Tuerkel needle were studied in detail. They noted platelet production in 85 of 150 megakaryocytes examined, and concluded that in this disease the platelet production is apparently not inhibited. A special attempt was made to identify the vascular lesions in the bone marrow. Although none was seen, the authors felt this procedure should be investigated more thoroughly in the future. In addition, they felt that splenic mechanisms were not involved in this disorder.

Symmers and Barrowcliff [22] in 1951 reported a case in a 40 year old white man who had had a period of apparent spontaneous improvement during his 15 week illness. Nitrogen retention was seen early in his disease, a situation which later subsided, with a resultant temporary improvement in his condition. Transfusions, streptomycin and penicillin were used in therapy. In addition to the usual pathologic findings, organization of intracapillary thrombi caused a peculiar interstitial glomerular sclerosis. A few glomeruli revealed changes identical to those seen in disseminated lupus. The patient had a negative muscle biopsy nine weeks before death.

Wallace [23] in 1951 described two cases which may possibly represent this disease. Both patients died in acute renal failure and showed pathologic evidence of glomerulonephritis. One patient showed a fine purpuric eruption on his lower extremities, whereas the other had none. Neither patient had central nervous system manifestations which could not be accounted for by the uremia, nor were vascular lesions found in the brain. One patient showed lesions typical of periarteritis. The author considered that there may be milder forms of thrombotic thrombocytopenic purpura which may be confused with Henoch-Schönlein's purpura, acute nephritis, rheumatic fever and polyarteritis nodosa.

In 1951 Symmers and Gillett [24] reported a remarkable case in a 53 year old white man who gave a long history of silica exposure, followed by active pulmonary tuberculosis several years before his death. His clinical course was quite typical of active pulmonary tuberculosis, although marked hypertension was also present. He had no purpura and only very mild anemia. He died after a massive gastrointestinal hemorrhage. In addition to active pulmonary tuberculosis and arteriolonephrosclerosis, pathologic changes were seen which were compatible with platelet thrombosis, disseminated lupus erythematosus, the late sclerotic stage of sarcoidosis of the lymph nodes, and polyarteritis nodosa. This patient gave no history of sulfonamide or antiserum exposure. No mention is made, however, in regard to drug therapy for the tuberculosis. The thrombotic lesions were widespread, but not found in great numbers. The close etiologic relationship of the histogenesis of these diseases is suggested by the authors.

Hauser, Beyer and Burger [25] in 1951 reported a case in a 20 year old woman who died five weeks after the onset of headaches and weakness. Marked mental changes occurred during the last eight days of her life. The authors raised the possibility that acute neurologic and psychiatric illnesses of unexplained origin might well be caused by thrombotic thrombocytopenic purpura. The pathologic picture in the described case showed widespread typical lesions of the disease, except that the liver was spared and the kidneys were only slightly involved.

In 1951 Rackow, Steingold and Wood [26] reported a case in a 32 year old man who died 16 days after the onset of his illness. This patient on autopsy showed 300 c.c. of pericardial effusion, plus the usual extensive thrombotic changes, although they were not marked in the bone marrow, nodes or lungs. The authors suggested that liver biopsy might be feasible in patients with few purpuric findings. They also considered—but did not attempt—biopsy of the gums. They found endothelial proliferation in non-thrombosed vessels, but did not believe this was proof enough to say the endothelial changes were primary. However, because of the localization of the lesion to the arteriolar-capillary junction, they did feel that vascular damage may play some part "in determining the site of, if not actually causing, the thrombi."

In 1951 Meacham, Orbison, Heinle, Steele and Schaefer [27] reported their studies on two cases. One patient underwent a splenectomy, with remission of symptoms for a long period of time. She lived three years from the onset of her disease. The authors noted that the occlusive intra-arteriolar mass was associated with abnormality of the arteriolar wall, with the presence of the same amorphous, pink-staining material. Loss of both elastic tissue and smooth muscle in the affected vessel wall was noted with special staining technics. They observed that the vessel walls were often very thin and distorted. They felt that these microscopic findings could only be explained by "—degenerative change in the vessel wall and that the presence of platelet

thrombi alone would not be expected to produce such lesions." Association with collagen diseases was entertained.

In contradistinction to Singer's [9] observations, they found platelet production inhibition in one of their two cases. They suggested that the process is similar to the mechanism which produces idiopathic thrombocytopenic purpura. They felt it possible that an abnormal splenic mechanism was present in these two cases.

During the same year Beigelman [42] reported two cases of this disease in which there was considerable variation from the usual picture, in both the clinical and the pathologic aspects. Both patients died in congestive heart failure and showed no definite evidence of neurologic changes, purpura or icterus. Although the platelet count was low in one case, it was usually normal in the other. Of interest is the finding of a hypoplastic bone marrow in the former case, who on necropsy showed platelet thrombi in the heart only, although there were findings suggestive of lupus erythematosus in the spleen. In neither case can the pathologic findings suggestive of thrombotic thrombocytopenic purpura be considered anything more than incidental, although associated findings suggest an interrelation with the collagen group of diseases.

Barondess [1] in 1952 added three cases to the literature, bringing the total cases reported to 41. One patient had received tetanus antitoxin two weeks before the onset of his illness; another gave a history of three episodes of rheumatic fever in childhood. Splenectomy five days before death in one case caused no appreciable change in her downhill course. Subacute glomerulonephrotic lesions were seen in one of his three cases. Peripheral blood studies for L. E. cells were negative in the one case so examined. He suggested further search for this phenomenon in peripheral blood and bone marrow studies. He mentioned the possible relation in one of his cases to disseminated lupus erythematosus. He felt that thrombotic thrombocytopenic purpura "is a manifestation of a hypersensitive state," and emphasized that vascular injury is a salient part of the lesions. His review of the literature is thorough and instructive.

Cooper, Stickney, Pease and Bennett [28] in 1952 described two cases in which the diagnosis was confirmed before death by the demonstration of the vascular lesions on bone marrow aspiration. The paraffin sections of solid marrow spicules were stained with hematoxylin and eosin. Skin sections did not reveal the lesions, although they were noted in sections from the psoas and rectus abdominus muscles. The authors believe that the disease represents one of the collagen diseases.

Gendel, Young and Kraus [29] in the same year reviewed two cases, both in young men who showed sensitivity to penicillin, one during the first week of his illness, the other when the drug was used for therapy of the already advanced disease. The latter patient also showed Raynaud's phenomenon, which progressed to gangrene of the right great toe. Of great interest is

the fact that the same patient died in peripheral vascular collapse, an infrequent cause of death in this illness. Autopsy revealed, in addition to the usual findings, bilateral adrenal necrosis. The author reëmphasized the opinion of Meacham,[27] that the thrombocytopenia is more likely due to inadequate platelet formation than to their exhaustion by formation of platelet thrombi.

Comess and Cyamada [30] in 1952 reported a case of thrombotic thrombocytopenic purpura with associated malignant nephrosclerosis, acute pancreatitis and diabetes. This patient manifested no purpura, although there was marked platelet deficiency and moderate anemia. In contrast to the usual case, the vascular abnormalities were noted only in the heart and the pancreas.

In 1952 Orbison [31] presented a thorough study of the histologic sections of two cases previously reported by Meacham et al.[27] By the ingenious portrayal of serial sections he was able to reconstruct a three-dimensional reproduction of the involved vessels. He was able to identify dilatations of the arterioles in areas where the vascular lesions were seen. This included vessels of the brain, thyroid, liver, adrenals, kidneys, stomach, mesentery and heart. The aneurysms were of the cylindric type primarily, and involved the arteriolar-capillary junction. The elastic lamina was often missing, while aneurysms contained hyaline material covered by a single layer of endothelium. Degenerative and destructive lesions were also seen in vessels in which no aneurysms were seen. He classified the reported vascular lesions as follows: (1) the "prethrombotic" hyaline changes of Gore;[11,17] (2) focal destructive lesions; (3) destructive lesions associated with vascular occlusions or thrombi; (4) endothelial proliferation; (5) aneurysmal dilatations. He felt that the described isolated lesions were best explained by primary vascular injury by an agent which also causes thrombocytopenia and hemolytic anemia. He felt that the disease is a definite entity within the group of collagen diseases.

Tackett and Jones [32] in 1952 reported two cases of this disease, both in males. One patient had had a prior iridocyclitis which was treated by intramuscular milk injections shortly before the onset of his illness. The megakaryocytes were reported as normal. Only a few vascular lesions were seen in the bone marrow on fixed sections. The other case gave a four year history of pulmonary tuberculosis. He lived 10 days after the onset of weakness and mild headache, followed by aphasia. Interestingly no thrombotic lesions were seen in the lungs, even adjacent to the pulmonary tuberculosis. The authors discussed the resemblances of thrombotic thrombocytopenic purpura to other processes, including thrombocytopenic purpura, rickettsial diseases, certain allergic phenomena and the collagen group. They advised further investigation, particularly in regard to the possibility of an infectious etiology.

Symmers,[33] also in 1952, gave an excellent review of the American and

English literature to that time, and presented two cases of thrombotic thrombocytopenic purpura. The first man, aged 32, developed his first symptoms of weakness, vague aching and anorexia one week after a febrile cold. One week after the prodrome, anemia, purpura and mental changes occurred, resulting in his death two weeks later. Before his death his platelets had decreased from 210,000 to 4,000. Only after reëxamining the pathologic sections two years later was the true diagnosis realized. The author's second case was in a 27 year old man who suddenly developed central nervous system changes leading to his death 54 hours later. He had undergone an inguinal herniorrhaphy two weeks earlier. The patient did not survive long enough for complete hematologic studies, although increased urobilinogen and urobilin were found. Only a few petechiae were noted, although pallor was present. Typical vascular lesions were found in the brain, heart, kidneys and portal tracts. Many glomeruli showed patchy hyaline obliteration of some loops. This patient also had a small hemorrhage in the left caudate nucleus.

Blackman, Cohen and Watson [34] in 1952 reported a case of thrombotic thrombocytopenic purpura in a 35 year old white woman whose initial symptoms were generalized aching pain, particularly in the back, and smoky urine. Past history revealed that she had had episodes of rheumatoid arthritis 12 years and also six months before the onset of her illness. She rapidly developed a severe picture of hemolytic anemia, purpura and, later, central nervous system changes. Cold agglutination tests were negative, as was the Coombs' reaction. Muscle biopsy was normal, while the bone marrow showed platelet inhibition.

In 1953 Ritama and Virkkunen [35] described the disease in a white woman aged 31 years whose entrance complaints were headache, diplopia, speech disturbances, weakness, and bleeding from the gums. One week prior to her admission she had developed a sore throat and headache. Past history revealed that she had had rheumatic fever 10 years before, and active pulmonary tuberculosis three years before admission. After a spontaneous abortion six months before her final illness she had developed mild transient purpura. ACTH was used throughout her entire hospital course of 16 days, with a temporary improvement in her condition. Splenectomy was performed 10 days before her death. This procedure caused a very slight rise in her platelet count and no change in her clinical course. The pathologic lesions were widespread, including subcutaneous tissues, but none was found in the abdominal wall musculature. Active fibrocaseous tuberculosis was present in the left lung. Lesions which the authors felt were indicative of disseminated lupus erythematosus were noted in the skin, kidneys and other organs. They felt that the essential pathologic process was inflammation of the vessel wall, and that the basic disease was disseminated lupus erythematosus. In addition, from the histologic picture the authors pointed

out the similarity of this disease to primary atypical amyloidosis, and suggested a "close pathogenic relationship between these diseases."

In 1953 Vassar and Spain [36] discussed seven cases, two of which had previously been reported by Gore. Two cases showed no purpura, while one of these revealed no platelet reduction. A Coombs' test performed on one case was negative, with questionable blocking antibodies being found in another. Red blood cell fragility determinations were normal in the four cases examined. Autopsy revealed widespread lesions of the disease. Hyaline thrombi were found on the aortic and mitral valves in three cases, with adjacent eosinophilic degeneration of the valve substance. An occasional lesion extended from the afferent arterioles into the glomerular tufts. No findings of lupus erythematosus were noted. Bone marrow studies did not reveal the vascular lesions, although they were noted in striated muscle. The authors found histologic changes to support the tenet that the vascular lesions are primary.

In 1953 Green and Green [37] reported a fulminating case in a 64 year old white woman whose initial manifestations were mental changes and speech difficulties. The patient had suffered a fractured ankle three weeks before. No platelet formation was seen on marrow smears, and no vascular lesions were noted in the bone marrow studies. ACTH was given during the last week of her life, to no avail.

March [38] in 1954 reported a case and gave an excellent discussion of the historical background and evolution of ideas in relation to this disease. Autopsy studies revealed dilated and damaged vessel walls in relation to the intraluminal material. He stated the degenerated substance originates at the site of vessel injury and propagates down the lumen, with the addition of further vessel wall degeneration, and transudation of fluid from the blood. In addition, formed elements of fibrin may form a part of the thrombus, which is then rapidly endothelialized. He also emphasized a probable sensitizing factor as causing the original vascular lesions, although no such factor has been proved as yet.

In 1954 Revill and Wilson [39] reported a fulminating case occurring in a 38 year old white man who had suffered from ulcers of both legs for a period of six months. Local treatment had consisted of Propamidine cream, zinc and castor oil. At the time of admission the ulcers had healed and only an eczematoid rash remained. Prodromata included abdominal pain, vomiting and red urine. Autopsy studies of the bone marrow revealed no vascular lesions. Coombs' tests were negative. The authors entertained the possible relationship of this patient's illness to the dermatitis and medications.

Ellison and Lloyd [40] in the same year reported a case in a 46 year old white woman who lived for two months after the onset of weakness, frontal headaches and uterine bleeding. Direct Coombs' test and cold agglutinins were negative. Postmortem examination was restricted to the abdomen. Large amounts of hemosiderin were found in the spleen. The authors noted

many thrombotic changes in the cortex of the kidney, which they felt were venules, a rarely reported phenomenon in this disease. They were aware of previous studies by Orbison [31] in reference to aneurysms of the arterioles and the difficulty of identifying absolutely the type of vessel involved. They noted considerable ischemic fibrosis of the renal cortex.

In 1955 Laszlo, Alvarez and Feldman [41] reported a case associated with disseminated lupus erythematosus. This 33 year old woman gave an eight year history of intermittent arthralgia. The final stage of her disease was characterized by mental changes, fever and thrombocytopenic purpura. Autopsy findings were compatible with both diseases. An L. E. cell test was positive, while the Coombs' reactions were negative. The authors attributed the failure of response to ACTH in this case to the findings of thromboses, hemorrhages and focal necrosis in the adrenal cortex. They advised using cortisone rather than ACTH because of this finding.

Case Report

A 24 year old male married cook of Italian descent was admitted to the Fort Belvoir, Virginia Hospital on December 10 and died on December 28, 1955. On December 2 he noted tingling of the tips of the fourth and fifth digits of his left hand, not associated with any weakness or swelling. Ten days before admission he had received a routine influenza vaccine injection, without any local or systemic reaction. On December 2, after the paresthesias had occurred, he donated 500 c.c. blood. On December 5 he first noted generalized weakness and a low grade fever associated with a mild sore throat, nasal congestion and a slight cough. At the same time he noticed his urine was very dark in color. After continuance of symptoms for three days he reported to Sick Call, where he was given a prescription for a cough medication. He was observed daily from that time on. On December 10 a number of petechiae and ecchymoses were noted on his body. A tourniquet was applied to his left arm at this time and he developed many petechiae within a few minutes.

Past medical history revealed that this Army private first class had been stationed at McLean, Virginia, where he had worked as a cook. He gave no history of exposure to chemicals or drugs. There was no history of any serious illnesses or operations. He had never had jaundice, anemia, rheumatic fever, arthritis or skin disease. He gave no history of fava bean ingestion. The patient was married and had no children. There was no family history of jaundice, gall-bladder disease, anemia, bleeding tendencies or allergy.

Physical examination at the time of admission revealed a moderately pale and obese man whose oral temperature was 99° F. The pulse was 110; respirations, 20; blood pressure, 130/70 mm. Hg. A number of petechiae were noted on the soft palate, trunk and all extremities. Several large ecchymotic areas were noted over the shoulder blades and the right upper arm, while several smaller areas were seen on the thighs. There was no upper respiratory infection. The neck was negative for glands, goiter and stiffness. The heart was not enlarged and the tones were of good quality. A soft blowing apical systolic murmur was present. The lungs were clear. A slight amount of cough was noted from time to time, but there was no dyspnea or wheezing. The abdomen was moderately obese. The liver, kidneys and spleen were not palpable, nor were the areas tender. No adenopathy was present. The genitalia were normal. The extremities revealed no edema and there were no joint abnormalities. Neurologic examination was entirely normal. The sensorium was clear. The patient's clinical course is outlined in figure 1.

The admission blood count revealed 9,650 white cells. Differential count showed 71% polymorphonuclear leukocytes, 26% lymphocytes, 1% monocytes, 1% eosinophils and 1% basophils. The peripheral blood smears showed anisocytosis, poikilocytosis and marked polychromatophilia; there was one normoblast per 100 white blood cells; no target cells were seen. The hemoglobin was 6.5 gm.%; bleeding time (Duke), 1 minute; coagulation time (Lee-White), 7 minutes; sedimentation rate, corrected (Wintrobe), 13 mm./hr.; hematocrit, 19%. Urinalysis showed a specific gravity of 1.018, no sugar or albumin, 2 to 3 white cells and 30 to 50 red corpuscles per high power field. The color was dark amber and clear. Serologic test for syphilis was

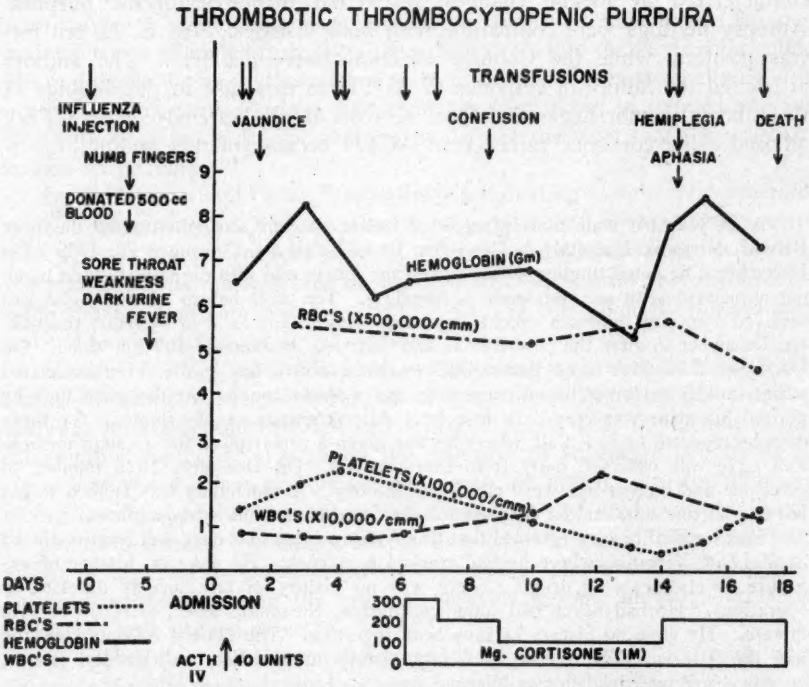

FIG. 1. Clinical course, laboratory findings and therapy in the reported case.

negative. The van den Bergh reaction was 0.58 mg.% direct, 4.32 mg.% indirect. The platelet count was 150,000. Mean corpuscular volume was 86 cubic micra, mean corpuscular hemoglobin was 31 mg., mean corpuscular hemoglobin concentration was 36%. Total blood protein, 6.46 gm.%; albumin, 3.77 gm.%; globulin, 2.69 gm.%. Clot retractility was 27 and 34% on two determinations, prothrombin time, 85%; fibrindex, normal; Coombs' test, negative. Red blood corpuscle fragility in hypotonic saline was normal. Adult-type hemoglobin was found by paper electrophoresis. Antistreptolysin titer was 12 units; C-reactive protein, 3 plus. Blood urea nitrogen was 26.9 mg.%. Chest film was normal.

The patient was given 40 mg. ACTH, along with 500 c.c. of blood, soon after his admission (figure 1). Within 24 hours of admission he became obviously icteric and remained so during the rest of his illness. In spite of repeated blood transfusions

there was no significant rise in his hemoglobin. The purpuric manifestations decreased slightly during the early days of his hospitalization. A low grade afternoon fever was present daily. Repeated platelet determinations varied between 10,000 and 225,000. On his sixth hospital day a bone marrow aspiration revealed increased production of the red corpuscle series. Megakaryocytes were present but appeared abnormal. Platelet production was not seen.

On his eighth hospital day he developed an episode of mental confusion, along with emesis of nonbloody material. He complained of noncramping epigastric distress and headache. Two days later he said that the persistent paresthesias of his left fingers were worse and that he could not use his hand properly. On his twelfth

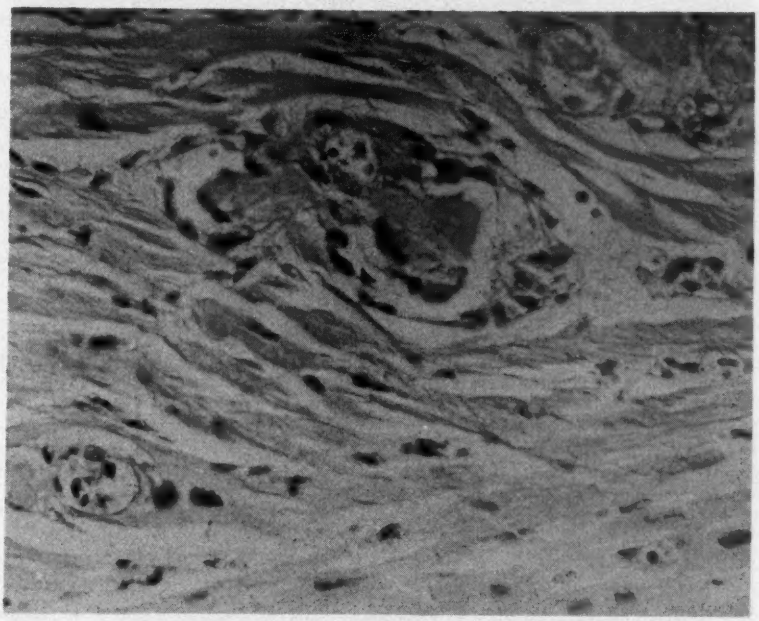

FIG. 2. Section of the heart, showing the typical obstructing vascular lesion apparently continuous with the blood vessel wall. × 350.

hospital day his condition became critical after he developed aphasia and a right hemiplegia which spared his face. New petechiae were noted, together with repeated minor epistaxes. His temperature rose to 104° F. The right arm remained flaccid and the plantar responses became positive on the right. A lumbar puncture revealed clear, colorless fluid not under increased pressure; the total protein was 116 mg.%, and the white cell count was 12.

His condition rapidly deteriorated and he died in coma on his eighteenth hospital day, 25 days after the onset of his first symptoms. Parenteral cortisone was given from the sixth hospital day until his death.

Autopsy was performed one hour after death (Dr. Pearse Meighan). The sclerae were icteric and the conjunctivae pale. Multiple purpuric spots were present over the trunk and extremities, together with several large ecchymotic areas. Moderate congestion of the lower lung fields was present. The pericardial sac contained

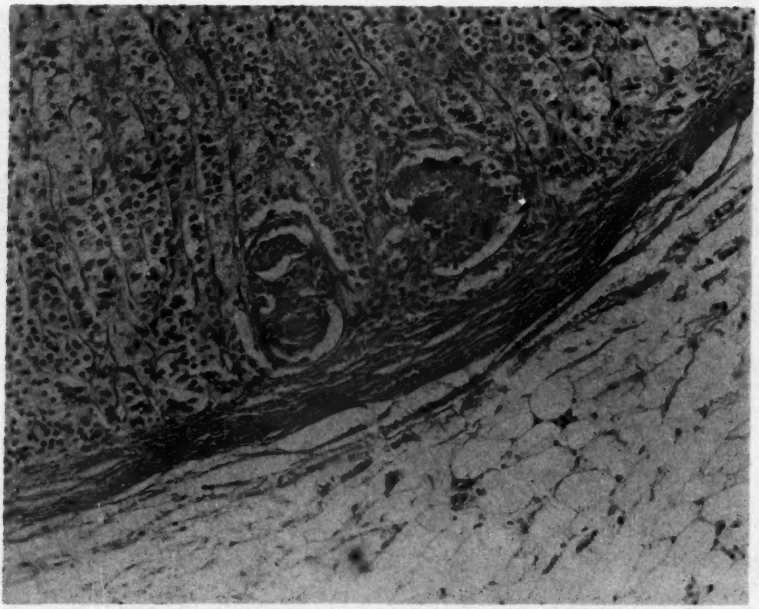

FIG. 3. Section of adrenal cortex, illustrating thrombus formation with partial obliteration of blood vessel lumina, and endothelialization of thrombus material. × 110.

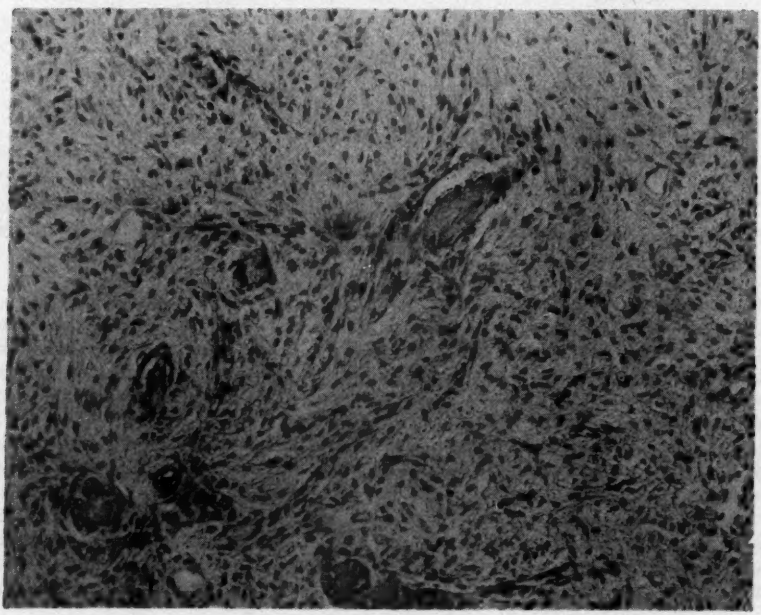

FIG. 4. Pars nervosa of the pituitary, illustrating the vascular lesion with occlusion, varying from partial to complete. × 110.

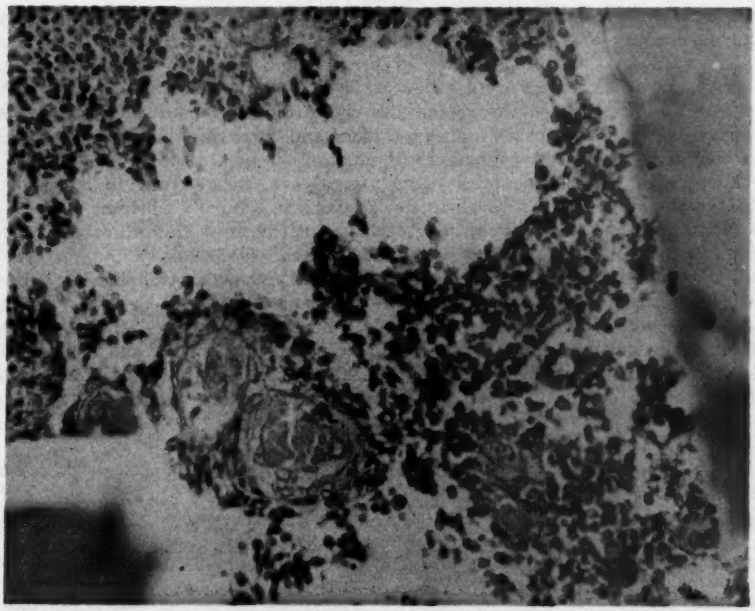

FIG. 5. Section of bone marrow, illustrating hyaline thrombi within the blood vessel lumina. × 240, H & E stain, fixed section.

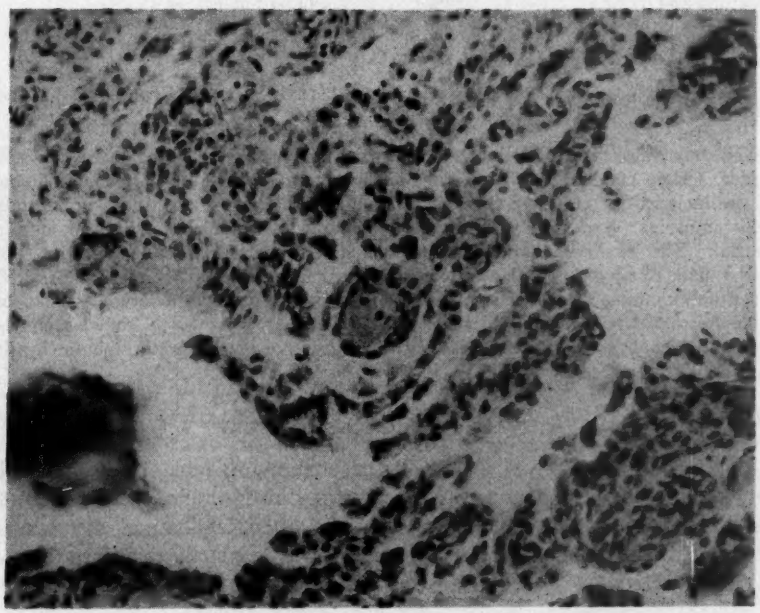

FIG. 6. Lung field, demonstrating a distended blood vessel occluded with hyaline amorphous substance. × 240.

125 c.c. of dark greenish fluid. The heart weighed 500 gm. and was covered with multiple purpuric spots. The epicardium showed a number of hemorrhagic spots. The endocardium showed a number of hemorrhagic areas, most marked in the auricles. The valve leaflets were yellow stained, but otherwise were normal. Multiple petechiae were noted throughout the myocardium. Hemorrhagic areas were grossly visible in the adrenals, kidneys, bladder and stomach. The liver and spleen were moderately enlarged, weighing 2,620 gm. and 420 gm., respectively.

Microscopic sections revealed many arterioles and capillaries to be involved with an eosinophilic, finely granular material which was usually adherent to one portion of the wall and almost completely occluded the lumen. This material in many instances was covered by a layer of endothelium. Occasionally the thrombotic material appeared to be undergoing organization, or perhaps an endothelial proliferation. The lesions were most numerous in the heart (figure 2), pancreas, and the zona glomerulosa of the adrenals (figure 3). Somewhat less involvement was seen in the kidneys, gastrointestinal tract, cerebral cortex, lymph nodes, and the posterior and pars media of the pituitary (figure 4). A moderate number of lesions was seen in bone marrow sections (figure 5), while the liver, spleen and lungs (figure 6)

TABLE 1

Prodromata of Thrombotic Thrombocytopenic Purpura

		Comment
Weakness and fatigue	65%	Earliest and most constant
Headache	45%	Often early, generalized, persistent
Mental changes	40%	Includes both subjective and objective
Anorexia and nausea	30%	
Vomiting	20%	Often from hemorrhage
Abdominal distress	20%	Usually not severe
Fever	15%	Primarily subjective; rare chills
Cough	12%	Usually nonproductive
Hematuria and dysuria	10%	Later findings, as a rule
Arthralgia	8%	
Numbness	7%	Never marked
Gastrointestinal bleeding	5%	

Other symptoms occasionally seen include substernal pain, tachycardia and vaginal bleeding.

showed only an occasional lesion. No vascular changes were noted in the prostate, bladder, testes, cervical cord, anterior pituitary and meninges. Associated abnormalities included increased number of eosinophils within the sinusoids of lymph nodes. These sinusoids were widely dilated and contained accumulations of pink-staining material. The glomeruli showed an occasional eosinophilic thrombus in the capillaries, while many subcapsular spaces contained erythrocytes. Many tubules were dilated and contained red blood cells, while others contained a smooth, homogeneous eosinophilic material. The pancreas was the only organ which showed smudgy eosinophilic changes within the vessel wall, suggestive of the prethrombotic hyaline changes first described by Gore.[17]

RÉSUMÉ OF CLINICAL FEATURES

The prodromata are varied. The accompanying table 1 illustrates the early symptomatology of the 63 cases reported in the literature. Weakness, mental changes, nausea, vomiting and, less often, abdominal distress are noted. Probably the weakness and malaise are primarily manifestations of developing anemia. Fever as an early symptom is only occasionally noted.

However, once the disease progresses to the purpuric stage, fever is almost always present to some extent. The mental changes, which are often seen early, are due primarily to the developing vascular lesions in the brain.

Purpura has been seen in all but 11 cases described in the literature. These findings usually appear a little later than the anemia, with a tendency to become gradually more marked. In addition to petechiae, many patients develop gastrointestinal bleeding, hematuria, epistaxis or ecchymoses. Vaginal hemorrhage may be seen. Pallor is generally pronounced by the time the patient is first seen, giving a striking contrast to the appearance usually noted in idiopathic thrombocytopenic purpura. The anemia may be very severe by the time of admission to the hospital. Icterus may be noted, but this is usually never marked during the entire illness.

TABLE 2

Physical Findings at the Time of Admission

	Degree of Involvement	Comment
Pallor	+ to ++++	Usually present
Fever	+ to ++++	Usually present
Purpura	+ to ++++	Present in 80%
Mental changes	+ to ++++	Present in 50%
Neurologic changes	+ to ++++	Present in 50%; no specific pattern
Icterus	+	Present in 50%; may be overlooked
Splenomegaly	+ to ++	Present in 25%
Hepatomegaly	+ to ++	Present in 25%
Hypertension	+ to ++++	Present in 15%; usually prior disease
Lymphadenopathy	+	Rarely seen
Arthropathy	+	Very rare; usually prior disease

++++ Very marked.
+++ Marked.
++ Moderate.
+ Slight.

The abnormal neurologic and mental changes are features in nearly all the reported cases. Early symptoms include generalized headaches, lightheadedness, dizziness and, occasionally, diplopia, paralyses and paresthesias. Mental changes range from lack of concentration to deep coma. Mania, hysteria, delirium, depression and convulsions have been reported. Especially characteristic is the variability of the neurologic abnormalities from day to day. Aphasia and hemiplegia are common. Peripheral neuritis has not been described. Eventually a majority of patients develop marked central nervous system changes which may lead directly to death.

General physical examination is not particularly distinctive except for the mental, hemorrhagic and anemic manifestations (table 2). In a moderate number of cases the liver and spleen may be palpable, but never enlarged to any marked degree. Rarely, lymphadenopathy may be found. There are no unusual cardiovascular abnormalities. Congestive heart failure has been reported in only two cases, although terminal pulmonary congestion is quite common. An occasional patient has had preëxisting hypertension, but usually the blood pressure is normal throughout the illness.

Laboratory studies show a rather marked anemia, usually with normal blood indices. The hemolytic character of the disease is suggested by increased blood bilirubin and urine urobilinogen, reticulocytosis and increased cellularity of the bone marrow in the red cell series, mild icterus, and the presence of normoblasts in the peripheral blood. In the few instances that liver function studies have been carried out little has been found to suggest hepatic insufficiency. The white cell count is usually not remarkable. Counts as high as 50,000 have been observed, but as a rule they are in the high normal range. Occasionally leukopenia is seen. There is some tendency for a shift to the left, although many reported differentials are entirely normal. Eosinophilia is not seen. The total white cell count has a tendency to rise as the disease progresses. The red cell fragility is usually normal with hypotonic saline. The L. E. reaction has been negative in all seven studies, except one with proved concomitant lupus erythematosus.[39] Coombs' reactions have been consistently negative in 15 cases, while mild hyperglobulinemia has been reported in several instances. Rarely, spherocytosis has been seen, and sicklemia has been present in only one case. Type A hemoglobin was found in the author's case.

The urine usually shows a mild proteinuria and varying amounts of hemoglobin and red cells. Terminal nitrogen retention is frequently seen but is usually not marked. The spinal fluid may show a mild pleocytosis and increased total protein, but signs of hemorrhage are rare. The spinal fluid pressure is normal or slightly increased.

Deficiency in platelets has been seen in nearly all cases in which this study has been done. The reduction is usually marked, but not necessarily so. There is a tendency for the count to decrease progressively during the course of the disease. A number of patients with platelet deficiency have not shown clinical findings of purpura. The bone marrow evidences of platelet production have been variously reported, but the recent literature suggests that malfunction of the megakaryocytes is usually present to a definite degree, although the total number of megakaryocytes is not altered to any significant extent.

The clotting and prothrombin time are normal, while the bleeding time may be prolonged. Clot retractility is impaired. Serologic tests for syphilis are negative. Blood culture, agglutination studies and other bacteriologic investigations are usually normal.

The pathology which involved the arteriolar-capillary junction has been adequately described in the literature review. The composition of the eosinophilic staining material which may be seen in the wall and usually within the lumen of the involved vessel has not been definitely ascertained. Apparently the process develops from primary damage to the wall of the vessel. Orbison [31] described the aneurysmal lesions associated with this involvement, while Gore [17] explained that isolated prethrombotic lesions were precursors to the fully developed pathology. All the major organs have been

involved, with special predilection for the vessels of the heart, pancreas and adrenals (table 3). Areas of ischemic necrosis have been described in all the major organs, but as a rule they are minimal. The hemorrhagic manifestations of purpura may be widespread, but cerebral hemorrhage such as is often noted in idiopathic purpura is rarely seen. Associated pathologic changes may be found, but are not usually characteristic. Several cases have been described with polyarteritis nodosa or lupus erythematosus. A considerable number of cases have glomerular lesions, some described as proliferative glomerulitis and others as glomerulonephritis. Their association with this disease is not clear, but because of their frequency they deserve further investigation. Small pericardial effusions have been noted in several cases, including the author's case. Absence of involvement of the

TABLE 3

Distribution of Pathologic Lesions

	Degree of Involvement	Comment
Heart	++++	Widespread
Pancreas	++++	
Adrenals	++++	Zona glomerulosa
Brain	+++	Cortex primarily
Kidneys	+ to +++	Variable involvement
Gastrointestinal tract	++	
Spleen	+	May be negative
Liver	+	May be negative
Bone marrow	+	May be negative
Lungs	+	May be negative
Skeletal muscle	+	May be negative

++++ Very marked.
+++ Marked.
++ Moderate.
+ Slight.

anterior lobe of the pituitary was described by Goldenberg et al.[19] A similar observation was noted in the author's case. Active pulmonary tuberculosis has been present in three patients.

Thrombotic thrombocytopenic purpura must be distinguished from many other hemorrhagic disorders. However, the triad of severe hemolytic anemia, thrombocytopenic purpura and fluctuating neurologic changes is almost diagnostic. Only a few of the described cases are at variance with these findings. Thorough hematologic studies must be made to differentiate this condition from the effects of exposure to toxins, drug sensitivity, idiopathic thrombocytopenic purpura and disease causing bone marrow destruction.

The average age of the 63 patients described in the literature is 35 years (table 4). Thirty-two patients were between the ages of 20 and 40, while 24 were older than 40. The age range is between nine and 74 years. Eight patients were Negroes, and 34 of the 63 were female.

The possibility of earlier confirmatory diagnosis is intriguing. As the disease becomes better known the index of suspicion will rise, but absolute

proof depends on finding histologic evidence of the vascular lesion. Studies of Cooper et al.[28] with paraffin sections of the bone marrow aspirate established the antemortem diagnosis in two cases. No reports with punch biopsies of the bone marrow have been made, but this method should be considered in the future. Pathologic studies of bone marrow on autopsy specimens have reported failure to find the lesion in only a few of the cases. However, the bone marrow is often not extensively involved. In the author's own case, bone marrow lesions were found on paraffin sections taken at the time of autopsy, but not from aspirated material. Involvement of the splenic vessels is reported in almost all cases, but splenic biopsy would probably prove to be too hazardous and unreliable. Involvement of skeletal muscles has been reported in several cases, but the lesions are apparently

TABLE 4

(A.) Age Range (Based on 63 patients reported in the literature)

Age	No. Cases
Under 10	1
10–20	6
20–30	19
30–40	13
40–50	11
50–60	8
60–70	4
Over 70	1

(B.) Duration of Life (includes prodrome period)

Under 1 week	6	31 under 1 month
1–2 weeks	8	
2–3 weeks	7	
3–4 weeks	10	
1–2 mos.	14	
2–3 mos.	7	
3–6 mos.	6	
Over 6 mos.	5	

very scattered. Although further study is needed, muscle biopsy at the present time does not appear too promising. Needle biopsy of the kidney has not been attempted, but the kidney is usually more extensively involved than either the spleen or skeletal muscle. Kidney biopsies also run the risk of hemorrhagic complications. Biopsy of the gums has been considered by Rackow et al.[26] but has not been tried. The same authors also suggested liver biopsy.

The clinical course is almost invariably progressively downhill. One case reported by Meacham [27] had a long remission following splenectomy. Several other patients had partial and probably spontaneous remissions. Once purpura and anemia have been well established, the prognosis is death within three months and usually in less than one month. In a number of cases the pathologic process has been only part of their illness, with the symptomatology not being particularly characteristic and the cause of death possibly due to concomitant disease.

Treatment has been singularly unsuccessful. The clinical course and pathologic findings suggest that vascular lesions appear early and in a rapidly increasing number of vessels. Unfortunately there has been little opportunity to attempt splenectomy early in the disease, before irreversible and irreparable damage has taken place. Splenectomy has been performed in nine cases, usually when the patient's condition was terminal. ACTH and cortisone have been used to some extent, with no results. These drugs have been used primarily in the late stages of the disease. Autopsy findings of extensive adrenal necrosis in an occasional case would suggest that cortisone would be the more logical drug to use. Extremely large doses in the early stages of the disease should be tried. Transfusions are of no lasting benefit. Various antibiotics have been used without help, even in the early stages of the disease.

TABLE 5

Possible Inciting Factors
(More Than One in Several Cases)

	Number of Cases	Comment
Recent upper respiratory infection	9	
Skin lesions (discoid lupus urticaria, ulcers, cellulitis, tape dermatitis, etc.)	8	Present during or just prior to illness Does not include purpura
Old rheumatic fever	4	
Recent sulfonamides	3	
Active pulmonary tuberculosis	3	
Penicillin sensitivity	2	
Recent smallpox vaccination	1	
Recent influenza immunization	1	
Recent tetanus antitoxin	1	
Recent foreign protein injection (milk)	1	
Old rheumatoid arthritis	1	
Lead poisoning	1	
Recent iodine ingestion	1	
Purpura hemorrhagica in sibling	1	
Disseminated lupus in sibling	1	
Polyarteritis nodosa in sibling	1	

The etiology remains unknown. A number of possible inciting factors have been noted in the literature (table 5). The probability of an unusual allergic type of response is quite great. The author's case is an illustration of this point. This patient had received an influenza immunization three days before his illness started. He also had had a mild upper respiratory infection. The family history of illnesses such as lupus erythematosus, polyarteritis nodosa and purpura hemorrhagica also suggests an antigen-antibody type of response. Four patients have had previous rheumatic fever, while various types of dermatitis have been seen in nine. The pathologic picture shows primary blood vessel damage, with resultant formation of the occluding lesions. The hyaline material, although not definitely analyzed, suggests that the disorder belongs to the growing family of collagen diseases. The megakaryocytic abnormalities imply a platelet arrest

such as is seen in idiopathic thrombocytopenic purpura, which is usually caused by a sensitizing agent. The anemia is of the acquired hemolytic type, although no definite causative factors have been found in the blood. Further investigations must be made in order to prove an antigenic factor, but the indirect evidence compiled to date is quite convincing.

Summary

A review of the literature has been made in order to elucidate further the clinical pattern of thrombotic thrombocytopenic purpura, a disease which has only recently been recognized as a clinical entity. A case in a 24 year old man has been added to the literature. This case suggests the probability of an antigen-antibody response following the injection of influenza vaccine, tending to confirm the present theory in regard to the genesis of this disease.

Summario in Interlingua

Purpura thrombocytopenic thrombotic ha devenite un recognoscite entitate clinic solmente in recente annos. Iste morbo, que es uniformemente mortal, es characterisate per le triade clinic de anemia hemolytic, purpura thrombocytopenic, e varie anormalitates del systema nervose central. Le tableau pathologic monstra primarimente alterationes in le arteriolas, con le formation de thrombos hyalin que non es ben comprendite.

Es describite un caso de purpura thrombocytopenic thrombotic occurrente in un masculo de 24 annos de etate qui disveloppava le triade typic de symptomas post le injection de vaccino de influenza. Morte occurreva 28 dies plus tarde al fin de un curso de deterioration irresistibile.

Le analyse de 63 casos reportate in le litteratura revela que le plus communmente observate prodromos de iste morbo es debilitate e fatiga (65%), mal de capite (45%), alteration mental (40%), anorexia e nausea (30%), e vomito (20%). Le scala del etates se extendeva ab nove usque a 70 annos, con 43 casos reportate a etates de inter 20 e 50 annos. Possibile factores incitante include infectiones supero-respiratori (nove casos), lesiones cutanee, non incluse purpura (octo casos), ancian febre rheumatic (quatro casos), e recente sulfonamidos (tres casos). Duo patientes esseva sensibile a penicillina. Un caso occurreva post vaccination contra variola, un altere post immunisation a influenza.

Le plus commun constatationes al tempore del hospitalisation include pallor, febre, purpura, e alterationes mental e neurologic de varie grados. Hypertension e anormalitates del articulationes non es characteristic, durante que leve grados de hepatosplenomegalia es incontrate in 25% del casos. Le lesiones diagnostic del morbo es vidite le plus communmente in le vasos junctional arteriolo-capillar intra corde, pancreas, adrenales, cerebro, e renes. Minus frequente e minus marcate affectiones es notate in le vias gastrointestinal, hepate, splen, medulla ossee, pulmones, e musculo skeletic. Il pare que le lesiones se disveloppa intra le parietes vascular e que il es solmente como effecto secundari que illos obstrue le passage vascular. Le lesiones es coperite de un sol strato de cellulas endothelial. Le composition del material amorphe non es cognoscite.

Ni studios laboratorial ni studios histologic ha resultate in adequate indicios con respecto al etiologia del morbo. Anemia hemolytic e reduction del numeration plachettal representa le plus uniforme constatationes laboratorial. Existe nulle prova definite del formation de anticorpore, ben que megacaryocytos anormal con absentia

del production de plachettas es le regula. Anormalitates neurologic es probabilemente le effecto de numerose lesiones occlusive in le vasos cerebral.

Le tractamento es usualmente sin valor, ben que un caso experientiava un longe remission post splenectomia. Le prompte ablation del splen e un uso intense de cortisona es recommendate.

Le diagnose pote esser establite per recognoscer le characteristic triade clinic. Confirmation del diagnose per medio de technicas bioptic se ha provate generalmente pauco satisfactori. Le uso de sectiones paraffinate de aspiratos de medulla ossee o de biopsias es le plus promittente.

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INHALATION RADIOCARDIOGRAPHY *

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A method has been described previously for the determination of diastolic and residual blood volumes of the heart after intravenous injection of a radioactive tracer (gamma emitter), recording the time-concentration curve over the cardiac area by means of a scintillation counter.[1] The method has been applied successfully to the evaluation of diastolic and residual blood volume in the right ventricle of normal subjects,[2] using radioiodinated human serum albumin.

It has been pointed out [1] that the radiocardiogram obtained by intravenous injection of radioactive tracer cannot be used in the same way for the calculation of the left heart volume, because of the prediluting effect of the right heart and lung circulation. It was suggested that use of an inhaled, gamma-emitting tracer should provide a radiocardiogram of the left heart.

Methyl iodide labeled with radioactive iodine (I^{131}) has been found suitable for study of left heart hemodynamics in both normal and cardiopathic subjects.

Methyl iodide is a yellow liquid of density 2.279 at 20° C., with a boiling point of 42.5° C., vapor pressure of 331.4 mm. Hg at 20° C., and 483 mm. Hg at 30° C. In a stream of air it evaporates very readily at room temperature. Its solubility in water is 1.4 gm./L. at 25° C., and it mixes in all proportions with ether.

Pharmacologically, methyl iodide has been known as a slight vesicant, related to ethyl iodide, which has been used extensively in cardiac physiology. The present investigation was initiated by examination of the toxicity of methyl iodide in chickens and rabbits. Varied quantities of unlabeled methyl iodide were added to 2 L. of air in a flexible respiration bag and heated to 50° C. to promote vaporization. The anesthetized animals were connected by a two-way respiration valve to the bag containing the gas mixture and were allowed to breathe the vapor for six to eight minutes, without rebreathing. Inhalation of 400 mg. produced no detectable change. After inhalation of 4.5 gm., death occurred in six hours. Gross and microscopic §

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examination of the viscera of animals treated with sublethal doses provided no evidence of injury. After lethal doses, pulmonary edema and congestion of trachea and bronchi were found.

The results of the toxicity studies, and the specific activity of the product, led to the use of amounts of the order of 1 mg. in human subjects, with a safety factor in excess of 100,000.

Preparation of the Tracer

Radioactive methyl iodide was obtained by an exchange reaction between methyl iodide and sodium iodide ($CH_3I + NaI^{131} \rightleftharpoons CH_3I^{131} + NaI$). Twenty milliliters of a water solution of sodium iodide, with total activity of 0.1 curie, and 100 mg. of methyl iodide, were mixed in a 100 ml. flask, closed with a stoppered, water-cooled condenser and left at room temperature until equilibrium was reached (about 24 hours). The solution was then cooled in ice and the organic product was extracted three times with 10 ml. of ether each time, using a magnetic stirrer to mix the two phases. After separation, by means of a funnel, the product was stored in a rubber-stoppered bottle and the activity was measured. Sixty per cent of the I^{131} was exchanged and the specific activity of the MeI^{131} was 600 μc/mg. As required by the decay of I^{131}, the quantity administered to a patient varied from 0.05 mg. to 1 mg. to provide less than 20 μc of radioiodine per test. Absorption of the methyl iodide by the inhalation equipment reduced the dose actually received by the patient to about three quarters of this amount. Ether was used to dilute the tracer in order to permit accurate measurement of the amount of tracer used. Its low boiling point was important in providing rapid evaporation. The total amount of ether given each patient ranged from 0.2 ml. to 0.5 ml.

Counting and Recording Equipment

The equipment used for measuring the activity of the appropriate sites on the patients, or of the experimental material, included a scintillation counter, mounted for adjustment of angle and movement in vertical and horizontal planes, a stable power supply, a linear amplifier and pulsation discriminator, a rate meter and a recorder. In most human experiments the counter was adjusted to the heart level of the seated subject. The gamma rays of the tracer activated the NaI (T1) crystal (1.5 by 1.5 inches) of the scintillation counter. The pulses induced in the photomultiplier tube were amplified, discriminated and fed into a counting rate meter with a time constant of 0.3 second. The activity was then recorded, using an Esterline-Angus pen recorder, so adjusted that 20,000 (20 k) counts per second produced a full-scale response.

The lead shielding of the scintillation counter was designed and constructed for this particular application, with the characteristics shown in figure 1. The aperture was chosen to avoid lung background without

appreciable loss of counting efficiency over the heart. As is shown in the figure, the resolution of the counter is 12.5 cm.

For some in vitro measurements, a well-type scintillation counter was used.

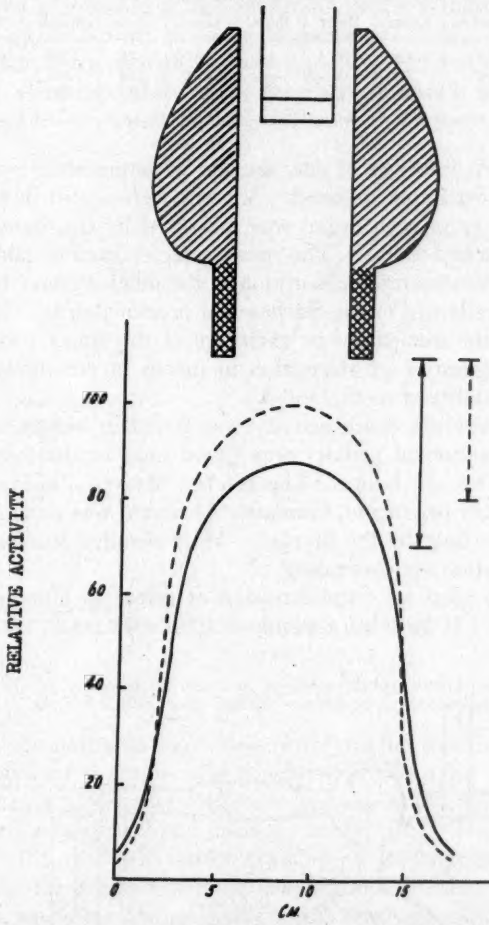


FIG. 1. Lead shielding of the scintillation counter and variations counting rate obtained by moving a standard source on a line perpendicular to the axis of the counter at uniform speed. (Continuous line—distance, 10 cm.: dotted line—distance, 7 cm.)

ABSORPTION OF METHYL IODIDE

The absorption of the active tracer was examined in animal experiments and in studies on human volunteers. Chickens and rabbits were used to study the absorption and body distribution of labeled methyl iodide. The respiration equipment and procedure employed were those described for the

TABLE 1

Distribution of Activity in Rabbits after Inhalation of Labeled Methyl Iodide

Time from Inhalation	Activity per Gram (Trachea Taken as Unity)									
	Kidneys	Trachea	Lungs	Heart	Brain	Liver	Bone	Muscle	Fat	Thyroid
1 hr.	.33	1	.23	.16	.14	.15	.14	.10	—	—
6 hrs.	.90	1	.28	.19	—	.171	.14	.06	—	19.91
24 hrs.	.07	1	.05	.004	.02	—	.01	.00	.01	1.29

toxicity studies. At intervals of one, six and 24 hours after treatment, the animals were sacrificed and dissected. Viscera were sealed in polyethylene bags and the activity of each organ was measured by the standard scintillation counter described above. The results are reported in table 1.

These studies demonstrated absorption of the inhaled tracer by the blood and its marked persistence in the trachea and bronchial tree. In these respiratory passages the dissipation or exchange of the tracer proceeded at a very slow rate, suggestive of absorption in mucus, a possibility consistent with the water solubility of methyl iodide.

In all periods studied, much activity was found in kidney and trachea. A greater concentration of activity was found only in the thyroid, which surpassed them after six hours. The trachea showed the lowest rate of loss of activity of any organ and, even after 24 hours, was exceeded in activity per unit weight only by the thyroid. More detailed studies of concentration and elimination are continuing.

The equipment used for administration of tracer to human subjects is shown in figure 2. It included a standard anesthesia mask, an evaporation

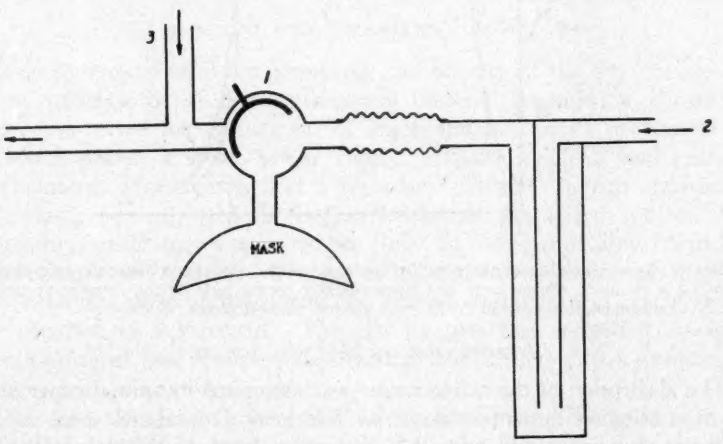


FIG. 2. Schematic representation of the equipment used for inhalation experiments in humans. 1 is the hand-controlled valve connecting the mouthpiece to either the active or the inactive side. 2 and 3 are one-way valves whose direction of flow is shown by arrows.

chamber for the tracer, a two-way valve, and rubber anesthesia tubing for connection of the major components and provision of an exhaust pathway. Minimal length of tubing between evaporation chamber and mask was found to be important.

With the active side of the apparatus closed at both ends, by valves 1 and 2, 0.2 ml. to 0.5 ml. of ether, containing 0.05 mg. to 1 mg. of methyl iodide, with activity up to 20 μc, was rapidly introduced into the evaporation chamber. The temperature of the chamber was raised to 50° C. by a water bath to complete evaporation and diffusion throughout the system in one

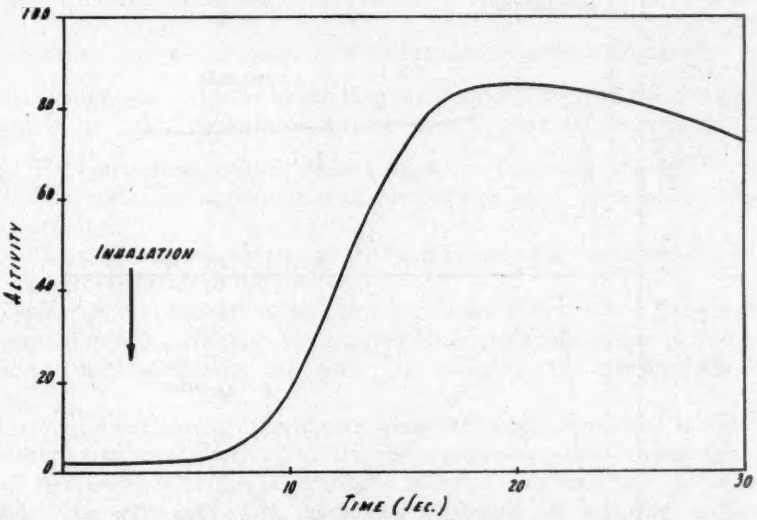


FIG. 3. Activity recorded in the hand of a normal subject after inhalation of radioactive methyl iodide, with activity expressed in arbitrary units.

minute. The anesthesia mask was fitted to the face of the patient, who breathed room air through valve 3, with expired air led out of the room by the exhaust tube. After a complete forced expiration, valve 1 was turned to close the two-way system and open the active side. The patient was asked to make a full forced inspiration, drawing air through the one-way valve 2 and carrying the tracer from the evaporation chamber to the lungs. At the end of a single inspiration, valve 1 was returned to the original position. The efficiency of transfer of the tracer, checked by Geiger monitoring of the evaporation chamber, was about 70%.

Evidence of absorption of radioactive methyl iodide by the blood consisted of several observations, including:

1. Scintillation monitoring, showing distribution of activity throughout the body a few seconds after inhalation of the tracer.
2. Urine collections in the first 10 minutes after inhalation, showing high activity.

3. Monitoring of the thyroid, which showed activity shortly after inhalation, and reached maximal activity in 24 hours.
4. Sampling of venous blood 10 to 15 seconds after inhalation, yielding appreciable activity.
5. Recording of hand activity curves, which demonstrated high concentration of activity in the hand 12 seconds after inhalation.

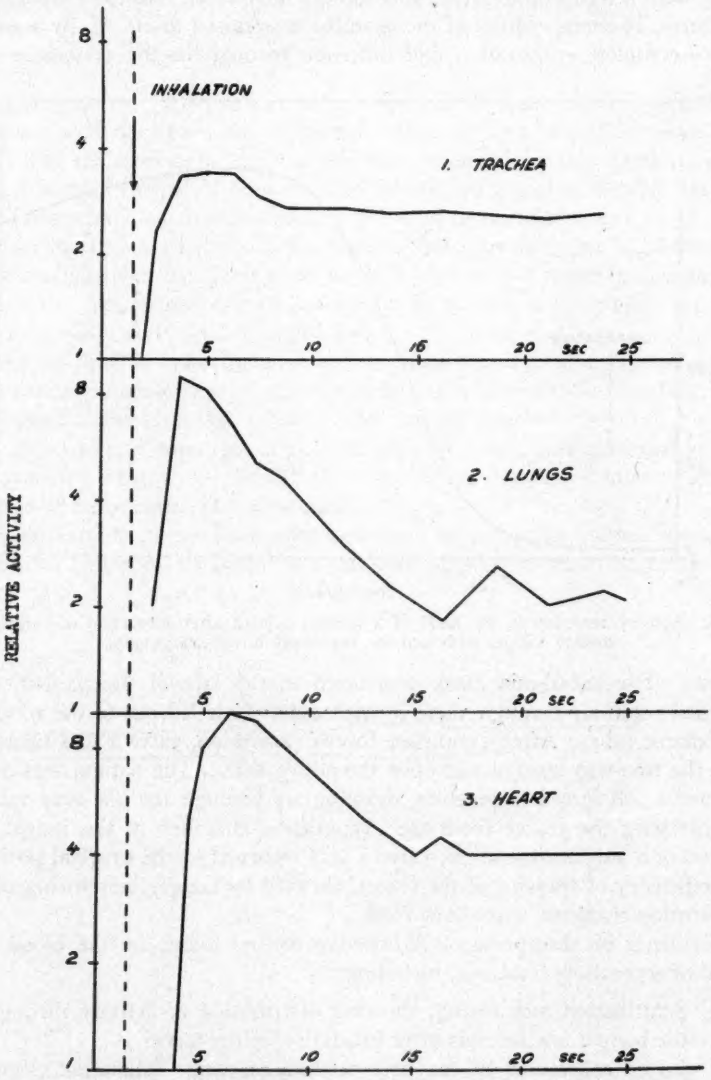


FIG. 4. Semilogarithmic representation of trachea, lung and heart curves.

This hand recording was obtained by wrapping the hand of the subject around the unshielded scintillation counter. A lead wall, with an opening adequate for the arm, protected the counter from the background activity of the patient's body. Figure 3 shows a typical curve. Activity appeared in the hand seven to 12 seconds after inhalation, reached a maximum in about 20 seconds, and decreased very slowly. These experiments demonstrated rapid absorption of methyl iodide by the blood and extensive diffusion into the extravascular space. The tissue-space diffusion indicated by the slow decline in activity of the hand suggests marked reduction in activity of the venous outflow.

Distribution of Activity in Respiratory System and Heart

To examine the influence of the lung and bronchial tree on the changing activity of the heart, measurements were made at three reference points:

1. The manubrium, considered as a measure of tracheal activity.
2. The right infraclavicular area, considered as a measure of lung activity.
3. The cardiac area, centered at the fourth intercostal space and the left edge of the body of the sternum.

Typical curves obtained at these sites are shown in figure 4. The curves represent different patients, who received different actual doses of tracer. Arbitrary units of activity are shown to emphasize the semilogarithmic plotting.

Four series of paired experiments were performed in normal subjects, recording variations of activity on the above reference points, changing the site of measurement or the experimental technic. For each test, 15 μc of methyl iodide were used, with the second inhalation and test three to five minutes after the first. The major features of each series of experiments are listed below:

First Series: first curve on point 1 (trachea), second on point 2 (lung).

Second Series: both curves on point 2 (lung), with free breathing after first inhalation and voluntary apnea after second inhalation.

Third Series: first recording on point 2 (lung), second on point 3 (heart).

Fourth Series: both curves on point 3 (heart), with free breathing after first inhalation and voluntary apnea after the second inhalation, as in the second series.

1. Comparison of Tracheal and Lung Curves: Activity in the trachea reached a maximum two seconds after the start of inhalation. For 1.5 to 2 seconds longer this level is maintained, and a rapid decline follows to a level of about 70% of the peak. This level then remains quite steady or declines

very slowly. The peak appears to result from the passage of the tracer through the trachea, while the high persistent level indicates residual activity absorbed on the tracheal mucus, as discussed in the description of the animal experiments. This view is favored by a comparison with the infraclavicular curve, which represents lung parenchyma.

This infraclavicular curve, taken at point 2, differs markedly from the tracheal curve. Peak activity is reached at about the same time, but activity decreases much more rapidly, as is seen in figure 4. In the same figure the lung curve, plotted semilogarithmically, shows a roughly exponential descending limb. Following this exponential portion, a steady or slowly decreasing level is reached. Analysis of tracheal curves and of animal data suggests that this persistent level derives from persistent residual activity in the bronchial system.

The data for the lung reported in table 2 show:

1. The peak times of activity.
2. The rate per cent per second, R_L, calculated from the slope of the recorded curve.*
3. The rate per cent per second for the rapidly exchangeable activity of the lung, calculated by subtraction of the persistent background † (bronchial in origin).

* An exponential function is expressed by $C = C_0e^{-KT}$ where C_0 is the initial (or peak) activity, C is the activity at time T, K is a constant, e is the base of natural logarithms, with a numerical value of 2.7183.

By rearranging the equation, one obtains:

$$C/C_0 = e^{-KT}$$
$$\ln C/C_0 = -KT.$$

This means that plotting the logarithms of activity against time yields a straight line, with a slope equal to $-K$.

At the half-time, when T is expressed in seconds:

$$C = 1/2C_0$$
$$\text{and, } \ln 1/2 = -KT_{1/2}$$
$$\text{or, } 0.693 = KT_{1/2}$$
$$\text{and, } K = \frac{0.693}{T_{1/2}}.$$

This constant, K, which we call slope (neglecting the minus sign of the real slope), is not equal to the rate per second. The rate per second is 100 times the relative decrease per second and is calculated as follows:

$$C_1 = C_0e^{-KT_1}$$
$$C_2 = C_0e^{-KT_2}$$
$$C_1 - C_2 = C_0e^{-KT_1} - C_0e^{-KT_2}$$
$$\text{and } T_2 = T_1 + 1 \text{ second}$$

or

$$C_1 - C_2 = C\,e^{-KT_1}(1 - e^{-K})$$
$$C_1 - C_2 = C_1(1 - e^{-K})$$
$$\frac{C_1 - C_2}{C_1} = 1 - e^{-K}$$

and the rate % per second is equal to $100(1 - e^{-K})$. The absolute rate itself varies with time and concentration. Consequently, it cannot be expressed by a single figure. Only the relative rate can be so expressed.

† Mathematically, the subtraction of a steady or slowly decreasing function from a perfect exponential function does not yield another exponential function. However, our corrected

TABLE 2

Curves Recorded on the Right Infraclavicular Area (Lung Curves) in Normal Subjects

No.	Peak Time Sec.	R_L % per Sec.	R^0_L % per Sec.	L_0/A_0
1	2.0	2.1	6.9	.62
2	2.5	9.2	15.4	.70
3	2.5	5.6	8.0	.73
4	2.5	15.4	17.3	.85
5	2.5	7.4	11.1	.58
6	2.0	7.9	12.2	.67

4. The fraction, L_0/A_0, where A_0 is the peak activity and L_0 the rapidly exchangeable activity at the same time.*

Table 2 shows the wide variation of the rate, R_L, from 2.1 to 15.4%/sec. Subtraction of the persistent activity component reduces this variation, with R^0_L between 6.9 and 15.4%/sec. The average exchangeable activity (L^0) is about 70% of the total activity (A^0).

TABLE 3

Curves Recorded on the Right Infraclavicular Area (Lung Curves) in Normal Subjects during Free Breathing (F) and in Apnea after Inhalation (A)

No.	Peak Time Sec.		R^0_L % per Sec. F	r^0_l % per Sec. A	d%	L_0/A_0 F	l^0/a^0 A	d%
	F	A						
1	2.0	2.0	15.4	31.2	+100	.80	.65	−19
2	2.5	2.5	20.6	28.8	+ 38	.78	.68	−13
3	3.0	2.5	20.4	32.0	+ 56	.72	.60	−17
Mean	2.2	2.3	18.8	30.6	+ 66	.77	.64	−16

2. Comparison of Lung Curves in Free Breathing and Apnea: The slope of the lung curve may have at least two components: first, the absorption and transport of the tracer in blood, and, second, the expiration of the tracer. To examine the relative importance of the two components, the second series of experiments was designed, with results reported in table 3 and typical curves for one subject shown in figure 5.

points fall along a straight line when plotted on semilogarithmic paper. It is only when the absolute corrected value is less than half the bronchial background that any substantial deviation from an ideal exponential function is seen. Therefore, in calculating the slope, these deviations were neglected.

* In all calculations, the notations used were:

R = rates calculated from recorded curve.
R^0 = rates calculated from corrected curve.
A^0 = activity recorded at peak time.

The subscriptions used were:

L = lung.
C = heart.
B = systole.

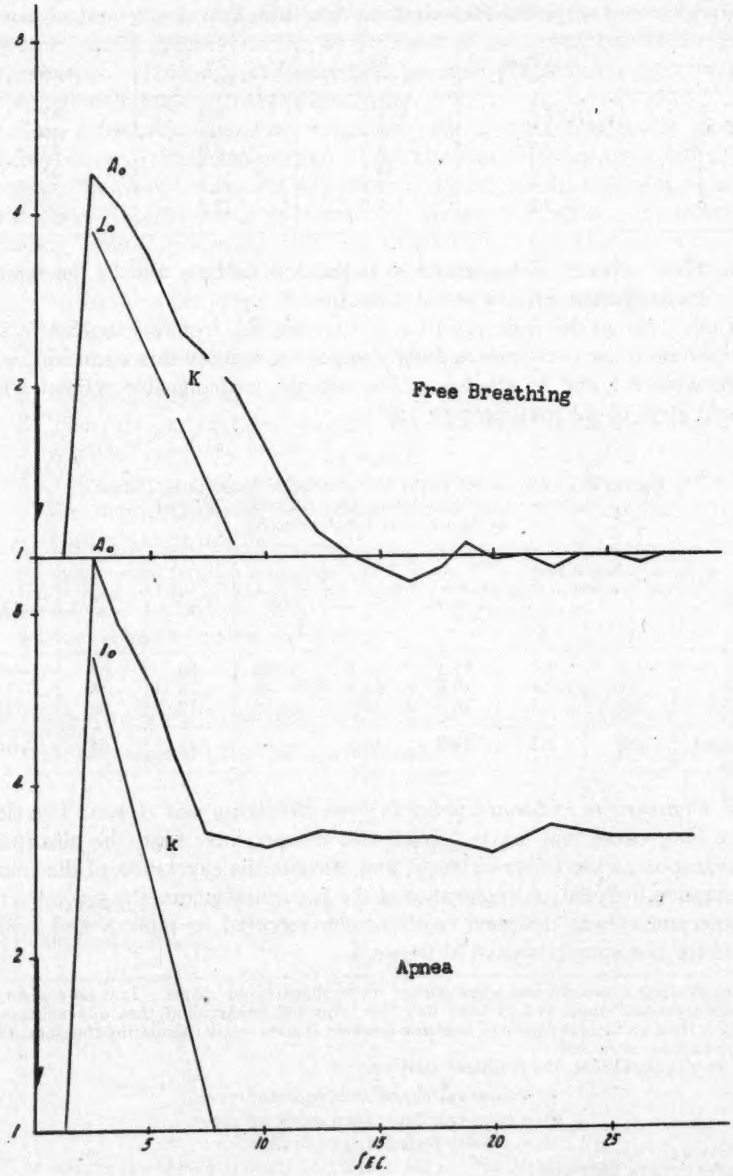


FIG. 5. Lung curves on one subject.

It is clear from these results that the total decrease in activity after the peak is smaller and of shorter duration in voluntary apnea than in normal breathing. The calculated exchangeable fraction (l^o/a^o) is smaller in apnea than is the same fraction (L^o/A^o) in normal breathing, and the relative rate, r^o_l, is faster than R^o_L.

Two processes may influence the rate of elimination in apnea: first, diffusion of tracer from air to blood and, second, transport of tracer out of the counter field by venous circulation. The measured slopes establish an average disappearance rate of 30%/sec.

TABLE 4

Comparison between the Curves Recorded on the Right Infraclavicular Area L and the Ones Recorded on the Cardiac Area C in Normal Male Subjects

Exp.	R^o % per Sec.	R^o_C/R^o_L	Peak Times Sec.
L	6.9	3.55	2
C	24.4		5
L	15.4	1.96	2.5
C	30.2		4.5
L	8.0	2.67	2.5
C	21.4		4.5
L	17.3	1.42	2.5
C	24.5		4.0
L	11.1	1.57	2.5
C	17.4		4.5
L	12.2	1.43	2.0
C	17.4		5.0

3. Comparison of the Lung Curve and the Heart Curve: This series of experiments was designed to examine the extent of reflection of the lung curve in the heart curve. The cardiac curve reached a peak four to five seconds after inhalation. This peak, always displaced to the right of the lung peak, was followed by a roughly exponential subsidence. Shortly, there followed a persistent or slowly decreasing level, similar to that seen in the lung curves.

Upon initial inspection, the heart curve differs from the lung curve in the delay of the peak and the shorter time between the peak and the start of the steady level. To clarify the features of both curves, they were analyzed by similar procedures, with the results shown in table 4.

1. R^o, the rate per cent per second calculated after subtraction of the persistent level.
2. The ratio between heart and lung.
3. The peak times.

It is apparent that the relative rate of exchange obtained after subtraction of the steady level is consistently higher for the heart curve, with a mean ratio of 2 between heart rate and lung rate. These differences are statistically significant ($p = 0.01 - 0.001$).

4. Influence of Apnea on the Heart Curve: For additional comparison of heart and lung curves, paired experiments were performed with the counter on the cardiac site, recording in voluntary apnea and in free breathing, as had been done for the lung. The usual mathematical analysis of the curves has considered the peak times, and the rate per cent per second, calculated after subtraction of the persistent level.

TABLE 5

Heart Curves in Normal Male Subjects during Free Breathing (F) and during Apnea after Inhalation (A)

No.	Exp.	R^{p}_{L} % per Sec.	Peak Time Sec.
1	F	16.5	3.5
	A	16.5	3.0
2	F	22.0	5.0
	A	20.0	4.5
3	F	21.6	5.0
	A	22.0	4.5

The results, reported in table 5, show only slight differences between the two curves in peak time and rate. The fact that apnea changes the lung curve very markedly, but the heart curve very slightly, suggests that they reflect different processes.

Considered together, these experiments indicate:

1. Only a small fraction of the inhaled methyl iodide, averaging 16%, is expired.
2. An appreciable fraction of tracer remains in the respiratory tract, probably absorbed by the mucus of the bronchial wall, from which it is lost very slowly.
3. Absorption and blood transfer are rapid, with 70% of the absorbable activity removed from the lungs by the blood in three seconds.
4. The heart curve is not influenced by the lung activity to any significant extent.

STUDY OF THE HEART CURVE

Forty-seven young healthy volunteers (32 male and 15 female) were tested. The results for males and females are summarized in tables 6 and 7. In all cases the peak activity was reached between four and one-half and five

seconds after inhalation of the tracer. Immediately after the maximum, activity decreased exponentially. From the slopes of the descending curves the rates per cent per second, R_c, were calculated and are reported in the tables. The exponential decrease continued about five seconds after the peak, and the activity approached a persistent or slowly declining level.

TABLE 6

Results of the Heart Curves in Normal Male Subjects

No.	R_c % per Sec.	End Level %	$R\%_c$ % per Sec.	Pulse per Second	$R\%_b$ % per Beat	Peak Time Sec.
1	13.3	40	21.4	1.16	18.5	5.5
2	12.8	40	24.4	1.17	21.4	5.5
3	9.2	66	24.4	1.28	19.4	5.0
4	9.9	42	17.3	1.27	14.0	5.0
5	8.9	47	20.2	1.10	18.2	4.5
6	6.5	42.5	15.0	1.00	15.0	6.0
7	16.1	43	25.8	1.40	18.5	4.0
8	8.2	51	21.5	1.47	15.7	5.0
9	7.7	50	23.5	1.10	21.8	4.0
10	6.8	61	20.2	1.40	14.0	4.5
11	9.3	58	23.3	1.51	15.8	5.0
12	16.1	36	30.5	1.20	25.2	4.0
13	13.3	45.5	22.5	1.28	18.2	4.0
14	7.7	53.5	16.8	1.07	14.8	4.5
15	7.6	56	21.4	1.60	14.0	4.0
16	11.6	50	22.1	1.25	18.2	4.5
17	7.7	59.5	20.2	1.25	16.5	4.5
18	29.0	20	30.5	1.60	19.4	4.5
19	7.6	43.5	18.8	1.25	14.8	5.5
20	13.9	34.0	24.4	1.46	17.6	5.0
21	9.2	55	24.4	1.24	20.0	5.0
22	11.2	60	24.5	1.35	18.5	4.5
23	9.2	44	17.4	1.20	14.8	5.5
24	6.9	53	17.4	1.12	15.7	5.0
25	10.7	53	27.0	1.27	21.8	5.0
26	17.8	31.5	24.5	1.38	18.2	6.0
27	10.7	38	21.5	1.33	15.7	5.0
28	9.9	35	20.2	1.14	18.2	7.5
29	21.0	25	22.5	1.14	20.3	5.5
30	6.9	51	16.5	1.20	14.0	4.5
31	9.9	42	22.0	1.40	15.7	5.5
32	13.5	38	21.4	1.34	16.5	5.0
Mean	11.3	45.6	22.0	1.28	17.6	4.98
s	4.6		3.12	.45	2.4	—

The exponential part of the curve shows a high degree of consistency within each sex group. The average value of the rate for males is 11.3%/sec. ± 4.6%/sec., and for females, 13.3%/sec. ± 4.1%/sec., a sex difference on the borderline of statistical significance. This consistency contrasts strikingly with the individual variations of the slopes of the lung curves. A lag time of two and one-half to three seconds after the lung peak is characteristic of the cardiac peak. These factors suggest that the curves recorded on the cardiac area represent transit of tracer through the left heart.

The departure from exponential of the descending limb of the curve may be influenced by several factors, including recirculation of the tracer in the blood, the pulmonary vein, the myocardium, the lung parenchyma and the left bronchus. Of these, recirculation demands particular consideration, as it is of significance in injection radiocardiography. In the present studies it appears much less important when viewed in the light of two features, the time of the deviation and its magnitude.

This deviation from exponential occurs too early to be accounted for by recirculating tracer. As is reported above, activity occurs in the periphery about 10 seconds after inhalation. Deviation from exponential occurs about five seconds after the peak, or nine seconds after inhalation. These experi-

TABLE 7

Results of the Heart Curves in Normal Female Subjects

No.	R_C % per Sec.	End Level %	R^1_C % per Sec.	Pulse per Second	R^1_b % per Beat	Peak Time Sec.
1	14.4	48	30.5	1.50	20.6	5.0
2	16.1	31.5	25.2	1.26	20.5	4.0
3	23.0	53	37.0	1.43	27.6	4.5
4	17.4	51	35.0	1.53	24.7	5.0
5	13.1	50	30.5	1.42	21.8	4.5
6	9.9	62.5	26.0	1.63	17.8	4.5
7	11.0	50	20.6	1.20	17.9	5.0
8	13.1	43	24.4	1.26	19.8	4.0
9	8.9	45	22.2	1.26	18.2	4.0
10	13.9	50	31.0	1.23	25.8	4.0
11	12.6	47	20.0	1.31	15.3	4.5
12	12.6	43	31.0	1.27	26.0	5.0
13	16.5	39	30.2	1.53	20.0	5.5
14	6.3	61	20.0	1.20	17.8	6.5
15	7.8	47	20.0	1.27	14.9	6.0
Mean	13.5	48	26.8	1.35	20.5	4.80
s	4.1		3.96	.15	4.0	—

mental values, and the commonly accepted values of 13 to 20 seconds for the general circulation time, eliminate recirculation as a component in the deviation. Further, it has been shown by Sutton, Karnell and Nylin [3] that tracer material injected by catheter into the pulmonary artery requires from seven to nine seconds to appear in the right ventricle. Even this short interval is greater than the five-second interval seen between peak and deviation. The figure of Sutton et al.[3] represents the shortest circuit, probably coronary circulation, which would return to the heart too small a fraction of the total activity to explain the deviation seen.

The magnitude of the deviation is another factor of importance. In our studies, the persistent or slowly decreasing level of activity following the exponential slope has a mean value of 48% of the peak. In the radiocardiographic experience of one of us,[4] after injection of radioiodinated human serum albumin (RIHSA), the steady level never exceeds 20% of peak value.

Another factor tending to reduce the importance of recirculation is diffusion of tracer into the perivascular spaces. The hand curves show that this is very extensive with methyl iodide. The venous return is thus depleted of activity by diffusion, and recirculation levels are reduced below the 20% level.

Exclusion of recirculation leaves the pulmonary vein as a possible circulatory component. Despite its anatomic relation to the heart this vessel cannot contribute to the post-peak deviation because its activity has been

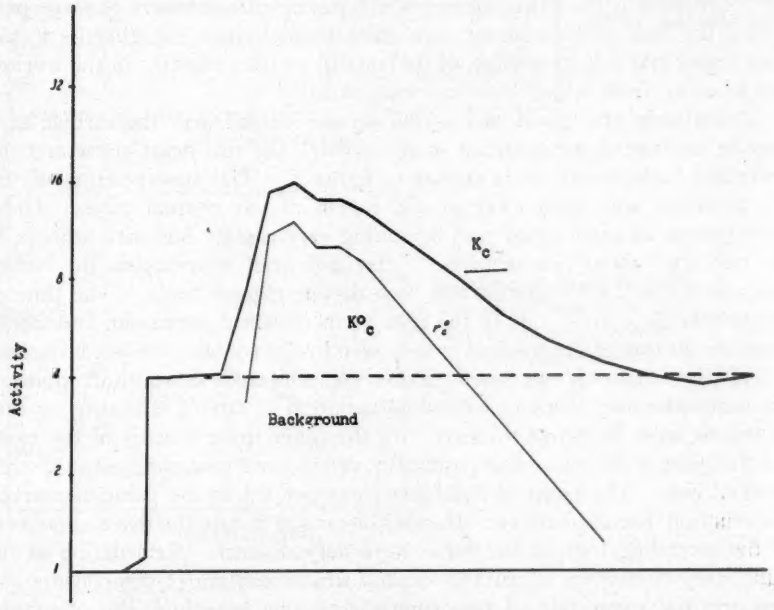


FIG. 6. *Heart Curve* (semilog). K^o_e is the slope of the real heart curve. Dotted line is total chest background. K_e is slope of recorded heart curve (before subtraction of background).

lost to the heart before the heart maximum occurs. Even before the heart peak, the contribution of the pulmonary vein must be small because its velocity is so great in relation to the 0.3 second time constant used. As has been demonstrated in a previous report, any preventricular volume cannot influence the slope of the heart curve, which is purely ventricular.

After elimination of the circulatory factors, there remain the lung parenchyma, left bronchus and myocardium tissue space. The influence of the lung parenchyma may be considered by examination of the anatomic situation of the counter and of the lung curves. The counter field includes the root of the lung, rather than a large volume of parenchyma. As the

methyl iodide appears to be evenly distributed throughout the lung volume, this small volume of parenchyma in the counter field can contain only a small fraction of the total activity, a fraction too small to account for the 48% value found for the persistent level.

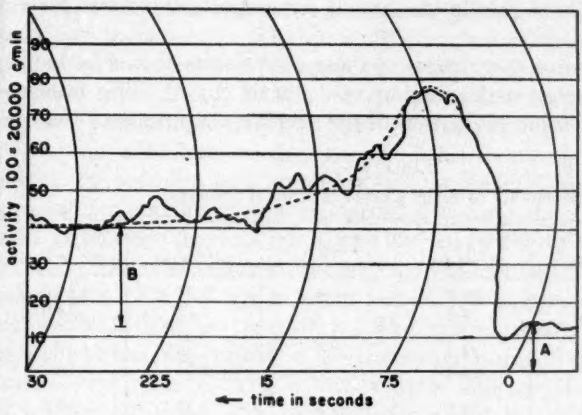
The fact that apnea changes the lung curve very markedly but the heart curve minimally shows that the heart curve is independent of variation in the lung curve and that the persistent level cannot result from activity in lung parenchyma.

The fourth factor considered a possible component of the deviation of the heart curve is the left bronchus, which lies behind the heart, in large part within the field of the counter. In animal and human experiments it has been found that a large portion of the inhaled activity remains in the trachea and bronchi, from which it is lost very slowly.

Tentatively, the initial part of the curve recorded over the cardiac area may be considered the resultant of two factors, the real heart curve and the bronchial background, as is shown in figure 6. The superposition of the left bronchus was quite clear in one fourth of our normal cases. These curves show an interrupted rise, beginning very rapidly but with a break in the rise after about two seconds. After this brief interruption the curves rise again, reach a maximum, and then decline exponentially. The time of the first break corresponds to the time of the tracheal maximum and implicates the portion of the tracheal system seen by the counter, the left bronchus.

The fact that only one fourth of the cases showed a sharp interruption of the initial rise may relate to individual variation in rate of inhalation or rate of transit from bronchus to heart. In the other three fourths of the cases the first part of the curve was practically vertical and then changed to a more gradual rise. The point of inflection corresponded to the point of marked interruption discussed above. In cases of cardiac failure the two components of the ascending limb of the curve were very distinct. Retardation of the pulmonary circulation appears to explain this separation of components and supports the suggestion of two components, one bronchial, the other circulatory.

An additional factor is indicated by anatomic considerations and the evidence of diffusion provided by the hand curves. This is persistent activity in the myocardial tissue spaces, introduced through the coronary circulation. The magnitude of this factor has not been determined, but it appears that it should exhibit the pattern of the diffused activity in the hand and persist for some time without substantial change. As the time used for calculation of the rate from the descending curve is less than five seconds, this persistent activity influences the curve in a manner identical with that of the bronchial activity and cannot be separated from it in our current data. For the present, the final persistent level in the heart curve may be considered as the resultant of two possible components, the left bronchus and the myocardial tissue space. The precise nature of this latter component does

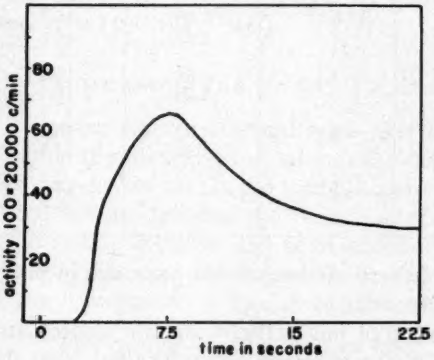


tracing of original record of normal female, table VII, no. 9

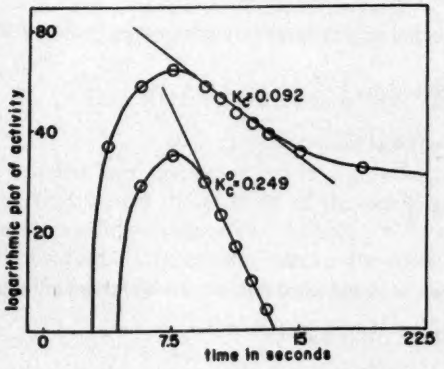
dotted line smoothed curve used for calculations

A - instrument background

B - total chest background



redrawing of smoothed tracing with normal time scale after subtraction of instrument background



logarithmic representation of curve before and after subtraction of total chest background

peaktime 4 sec.
pulse per sec. 1.26
background % 45
$R_c^o = 22.2$
$R_b^o = 18.2$
$R_c = 8.9$

FIG. 7.

not influence the mode of calculation, and is not important for our present purpose.*

However, the relative magnitudes of these components should be known to permit a more complete understanding of the heart curve. This information may also permit some estimation of the relative magnitude of the cor-

TABLE 8

Reproducibility of Heart Curves in Normal Subjects

No.	Rc % per Sec.	$R^{a}c$ % per Sec.	d%	Pulse per Second	R^{a}_{b} % per Beat
1a	12.6	31.0	4.9	1.27	24.4
1b	9.9	28.0		1.13	24.9
2a	9.2	24.4	0.0	1.28	19.1
2b	9.2	24.4		1.46	16.9
3a	16.5	30.2	2.3	1.53	19.7
3b	18.2	31.7		1.73	18.4
4a	6.3	20.0	0.0	1.20	16.7
4b	11.9	20.0		1.22	16.4
5a	17.8	24.5	3.1	1.38	17.8
5b	10.4	23.0		1.25	18.4
6a	10.7	21.5	4.9	1.33	16.2
6b	5.8	19.5		1.35	14.5
7a	9.9	20.2	5.7	1.14	17.7
7b	9.2	22.5		1.20	19.7

onary circulation in patients. Additional studies of this point are in progress, using both patients and animals.

In our calculations the dual nature of this background was ignored and a single background was used. This background was subtracted from the total curve to yield what we consider to be the true heart curve.

* If the background is due to activity that returns in front of the counter by means of coronary flow to the heart muscle, then:

the change in measured activity $\left[\frac{dA}{dt}\right]$ is equal to

the output minus a fraction of the output $\frac{dc}{dt}(1 - B)$

or

$$\frac{dA}{dt} = \frac{dc}{dt}(1 - B)$$

and by integration:

$$A = C_0e^{-Kt}(1 - B) + C_0B,$$

where C_0B is the integration constant for $t = c$, and equal to the total background due to absorption. By rearranging:

$$A - C_0B = C_0(1 - B)e^{-Kt}$$

or

$$\log_e (A - C_0B) = \log_e C_0(1 - B) - Kt.$$

The subtraction of the total heart background from the activity gives a straight line, with a slope K, the real slope of the heart output.

This subtraction was performed for the plotted curves of normal subjects, as shown in figure 7. The rates, R°_{c}, are reported in tables 6 and 7, together with other data concerning normal subjects. The mean values obtained were $22.0 \pm 3.12\%$/sec. in males and $26.8 \pm 3.96\%$/sec. in females. This difference is statistically significant (p 0.001).

To relate the loss of activity to the heart frequency, the half-time of the curves, in seconds, was multiplied by the heart frequency, in beats/sec., yielding the number of systoles needed to reduce the heart activity by one-half. The slope per beat was then obtained by the usual calculation 0.693/S1/2). The relative rates/beat are reported in tables 6 and 7. The average rate/beat is $17.6 \pm 7.6\%$ in males and $20.5 \pm 4\%$ in women, a statistically significant difference (p 0.001). The reproducibility of values obtained by subtraction was tested in seven normal subjects in whom two heart curves were recorded with a three-minute interval and with slight change of counter location. The results are reported in table 8. The mean absolute difference between the paired values is 3.1% and appears to be due to chance ($p = 0.5 - 0.6$).

Summary of the Unique Properties of the Heart Curves

Curves of three different types may be recorded on the chest after inhalation of radioactive methyl iodide. None of them is the pure expression of a single process. In the tracheal curve the lung component is not without effect, nor are tracheal and bronchial effects lacking in lung curves. The same factors influence the heart curves, with their bronchial background. However, the experimental results permit analysis of some unique properties of the heart curves. The three important characteristics are:

1. The cardiac peak is reached later than the tracheal and lung peak, three and one-half to five seconds after inhalation.
2. The rate is not affected by apnea.
3. Subtraction of the bronchial level yields constant values for the rate.

The Residual Blood of the Left Ventricle and the End-Diastolic Volume

It has been demonstrated in a previous report [1] that the slope of the heart curve expresses the fraction of the ventricular end-diastolic volume (VDV) corresponding to the stroke volume (SV) when the rate per cent is measured per beat, or to the cardiac output per second when the rate per cent is measured in seconds. The absolute value of VDV can be calculated:

$$VDV = SV/\text{rate}\%/\text{beat}$$

And the residual systolic volume, RSV, may be obtained:

$$RSV = VDV - SV$$

It has been shown [1] that atrial transit of tracer does not influence the slope appreciably, because normal atrial emptying approximates 100%/second.

Calculation of our values yields a stroke volume 17.5% of end-diastolic volume for normal men, with residual blood of 82.4%, and, in normal women, 20.5% and 79.5%, for the left heart.

Gigli and associates,[2] who measured the right ventricle volumes by tracer injection, reported for males a stroke volume of 23.1 ± 6% (residual, 76.9%), and 22.8 ± 2.06% for women.

The left heart results of the present study are of the same order of magnitude. The two groups of experiments cannot be compared too accurately, as the subjects were not identical and the recording positions were different, with those in left heart studies sitting and those in right heart studies prone. There appears, however, to be good agreement between the results, and no indication of marked differences in residual blood volumes of the two ventricles. However, a real difference may exist, as the differences are statistically significant for both sexes (p 0.001 for males, p 0.01 for females). It appears unwise to accept the apparent differences without further study of both sides in the same subjects under the same conditions. Until this is done, there remains a possibility of a systemic factor operating in both groups of observations to a different degree.

Absolute measures of end-diastolic and residual ventricular volumes for the left heart require measure of cardiac output, which was not obtained from these subjects. The commonly accepted values of stroke volume, 60 to 70 ml., permit estimation of the end-diastolic volume as 340 to 400 ml. for males and 300 to 350 ml. for females. Residual blood volumes calculated from these estimates are 280 to 330 ml. for males and 240 to 280 ml. for females. As pointed out previously,[1] and in figure 10, practically all of the heart volume for each side is represented by the end-diastolic volume, as atrial emptying is nearly complete. Addition of the right [2] and left mean values provides a total heart volume at the end of diastole (the maximal heart volume) of 700 ml. for males and 630 ml. for females, and postsystolic volume (minimal heart volume) of 550 ml. in men and 480 ml. in women.

Estimates are available for cardiac volume based upon anatomic studies and radiologic calculations derived from heart size by empiric formulae. The anatomic data show marked variability, with estimates of 85 ml. (Gray [5]), 90 to 120 ml. (Brash [6]), 137 ml. (Digerstedt,[7] Hochrein [8]), 200 ml. (Bucciante [9]), and 160 to 230 ml. (Chiarugi [10]). For atrial capacity, reports include 57 ml. (Gray [5]) and 110 to 185 ml. (Chiarugi [10]). The variability of these figures suggests that a number of artefacts may influence such results, and that their application to the living organ may not enjoy great confidence. Among factors which may influence anatomic estimates are cause of death, and time lapse between death and measurement and treat-

ment of the heart before and during measurement. The variability of the reports and the variety of fortuitous influences do not permit application of these measurements to the present problem of functional heart capacity.

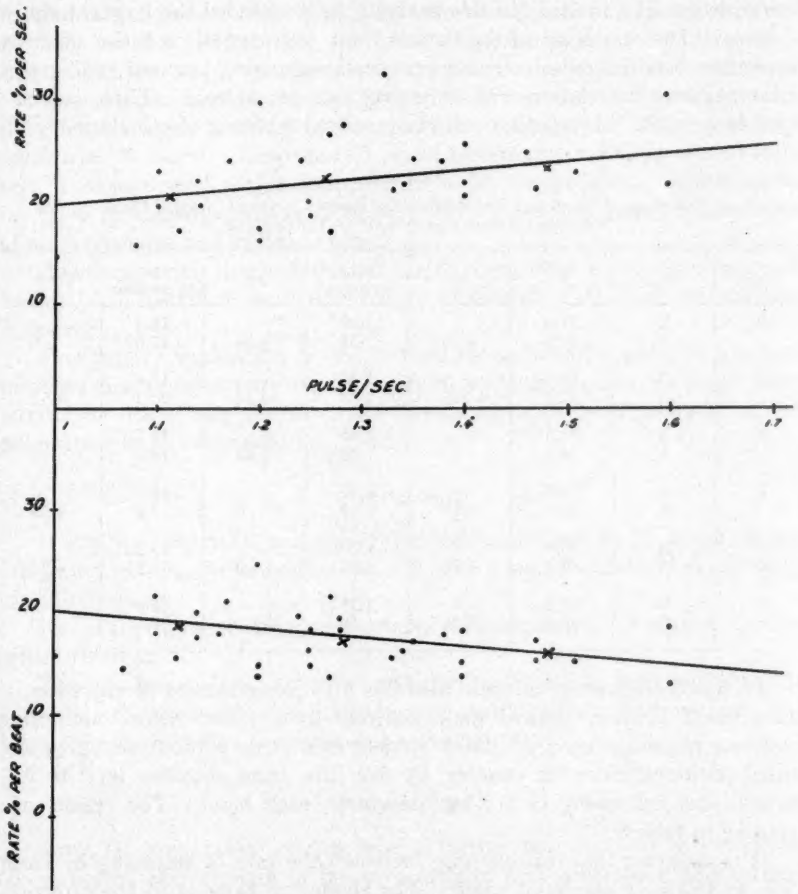


FIG. 8. Relation between pulse rate and rate of emptying. The crosses represent mean values of three groups (pulse rate, 1.0–1.2; 1.2–1.4; 1.4–1.6).

Radiologic estimates of heart volume, generally based on the biplane method of Liljestrand et al.[11] range from 520 to 860 ml. When the myocardial volume of 200 to 300 ml.[12, 13] is subtracted, these values are about 100 to 140 ml. below those calculated from radiocardiograms. This difference may result from several small errors inherent in the radiologic procedure, including the nature of the empiric formulae used and the mathe-

matical fact that a small error in measurement by orthoradiogram yields a much larger error in calculation of volume.

In figure 8, pulse rate per second has been plotted against rate % of ventricular emptying per second and rate % of ventricular emptying per beat. The male group was used for this analysis, as it included the larger number of cases. The scattering of the data is high, but suggests a linear positive correlation between pulse rate and ventricular emptying per unit time and a linear negative correlation with emptying rate per systole. These correlations support the theoretic basis of the proposed methods of calculation.

TABLE 9

Influence of Moderate Exercise on the Heart Curves of Normal Male Subjects—Before Exercise, B; After Exercise, A

No.	Exp.	$R^{\%}_{c}$ % per Sec.	d%	Pulse per Second	d%	$R^{\%}_{b}$ % per Beat	d%
1	B	24.4		1.00		24.4	
	A	30.3	+24.1	1.34	+34	22.6	−9
2	B	17.3		1.27		13.6	
	A	37.2	+115	1.83	+44	20.3	+51
3	B	21.5		1.47		14.7	
	A	24.6	+15	1.80	+23	13.7	−6
4	B	25.8		1.40		18.7	
	A	30.7	+19	1.40	0	22.0	+25
5	B	30.5		1.20		25.5	
	A	37.2	+22	1.20	0	31.0	+22
6	B	18.8		1.25		15.1	
	A	25.2	+34	1.30	+4	19.7	+30

To test the efficiency of these methods for discrimination of variation in heart blood volume, normal male subjects were tested before and after moderate physical exercise. Each subject exercised, without changing his seated position before the counter, by five lifts, from shoulder level to full vertical arm extension, of a 5-kg. weight in each hand. The results are reported in table 9.

It is apparent that this exercise increases the rate of emptying by from 19% to 115% of the basal value. The change of slope is in the direction expected, as cardiac output increases after exercise. When the cardiac output is measured at the same time, by injection methods, the present method of radiocardiography measures the two main factors influencing stroke volume, diastolic filling and systolic emptying.

SUMMARY

Analysis of left heart hemodynamics is essential for cardiovascular diagnosis. In current practice, the only method of study of intracardiac

hemodynamics is catheterization. This method has provided extensive and clinically important information of events in the right heart and in the pulmonary circulation as far as the capillaries. Recently, methods have been described for catheterization study of the left heart, but they offer danger to the patient and require delicate manipulation. Moreover, these methods measure pressure in the heart chambers and do not give direct information on the blood volumes and transport rates in the heart chambers.

The present method, in association with injection radiocardiography, provides a simple, harmless and reproducible tool for the study of the dynamics of the heart. Less than 25 μc. of radioactive iodine is needed for a test, a dosage well within permissible limits for patients. Simultaneous injection radiocardiography can be performed providing data for calculation of stroke volume and cardiac output.

As occasion may demand, the test can be repeated at appropriate intervals, as has been described, with intervening modification of heart performance if desired.

Preliminary application of this method in cardiopathic patients has been initiated and a preliminary report has been made at the Turin (Italy) Conference by one of our team.[1] (A full clinical paper is in preparation, for publication at an early date.)

Conclusion

It appears reasonable to suggest that radiocardiography by injection and inhalation technics, described above, will offer a valuable method of assessing cardiac function.

It also appears that radiocardiography will supplement, or replace, cardiac catheterization.

The low tracer dose and ease and rapidity of testing, together with the low cost of equipment and maintenance, make radiocardiography by the inhalation method a very simple and accurate test.

Addendum

Since the preparation of this report, further investigation in the rabbit has indicated that activity in the myocardium may contribute substantially to the final steady level of the inhalation radiocardiogram. (Debus, G. H., Donato, L. A., Nace, P. F., Moule, J., and Murrell, L. R.: The distribution of radioactivity in the rabbit after inhalation of methyl radioiodide or injection of sodium radioiodide, Minerva Nucleare, 1958, in press.)

Acknowledgments

The authors wish to acknowledge the generous assistance of Dr. L. E. Farr and the staff of the Department of Medicine of the Brookhaven National Laboratory in the selection of the tracer. Appreciation is also expressed to Miss Pauline Cookson, Mr. Leonard Murrell and Mr. John Moule for valuable assistance in this work.

SUMMARIO IN INTERLINGUA

Le studio del function e del disordines del corde dextere ha profitate grandemente del disveloppamentos recente de catheterisation intracardiac e de radiocardiographia a injection. Inherente characteristicas del systema circulatori ha prevenite le efficace application de iste methodos al corde sinistre. Le presente reporto describe un simple e salve technica que se ha provate efficace in le studio del corde sinistre e in le diagnose de congenite e acquirite lesiones cardiac in patientes human.

Le methodo provide accurate information quantitative relative al function del corde sinistre. Iste information es obtenite rapidemente e sin disconforto pro le patiente. Sedente ante un contator de scintillation, le patiente inhala—in un sol profunde inspiration—minus que 0,5 ml de ethere anesthetic. Solvite in le ethere es un micre quantitate de radio-ioduro methylic. Le passage a transverso le ventriculo sinistre de iste micre quantitate de materia radioactive (15 μc de I^{131}) es detegite per le crystallo del contator, e un curva que representa le passage es producite per un stilo-registrator connectite con le apparatura de contation.

Un curva normal pote esser distinguite ab un curva anormal per inspection visual. Le mesuration del declino del curva post su culmine provide le base del calculation del volumine per pulso, del volumine residue, e del rendimento cardiac.

In nostre gruppo experimental de masculos e femininas normal, le valores calculate esseva: pro masculos, volumine per pulso equal a 17,5% del volumine termino-diastolic, volumine residue equal a 82,4% del volumine termino-diastolic, e volumine termino-diastolic equal a 700 ml; pro femininas, le valores correspondente esseva 20,5%, 79,5%, e 630 ml. Le procentages es de alte signification pro studios experimental e pro objectivos diagnostic. Valores absolute de volumine pote esser obtenite per medio de radiocardiographia a injection in casos in que iste information es requirite pro objectivos special.

Le capacitate del technica a deteger alterationes del function cardiac esseva investigate in studios del effecto de exercitio in subjectos normal e per medio de mesurationes in patientes con cognoscite cardiopathias. Le resultatos de iste studios confirmava le valor del methodo. Le extension de iste analyse a un plus grande serie de patientes es in progresso e continua provider provas del utilitate clinic del methodo.

Le innocentia del technica esseva investigate plenmente in experimentos animal ante su application a subjectos human. Nulle effectos adverse ha essite observate in le curso de un anno de experientias. Isto non es surprendente, viste le facto que le dose de traciage, 15 μc, es ben infra le limites de securitate. Illo es simile al doses de traciage usate in studios thyroide pro que extensissime experientias clinic ha essite accumulate. Le activitate de 15 μc es administrate in 0,05 a 1 mg de ioduro methylic. Pro tener le dose al minimo extreme on se servi exclusivemente de fresc preparatos de traciage. Isto es possibile sin difficultate proque le production del preparato es simple. Le radioactive ioduro methylic es preparate per un simple reaction de excambio—in aqua—inter radio-ioduro de natrium (NaI^{131}) e ordinari ioduro methylic.

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THE EFFECT OF ANTECEDENT DIET ON URINE CONCENTRATING ABILITY *

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Diminished ability to concentrate the urine is considered to be an important criterion of renal disease, but the test most often employed to assess concentrating ability is subject to considerable variation and may be difficult to interpret.[1] The overnight dehydration test, a standard procedure in many hospitals, will usually yield a specific gravity of 1.022 or greater in the morning urine of a normal person.[2] When the specific gravity is less than 1.022, it is taken as evidence of diminished concentrating ability, and other examinations are performed to reveal other defects and establish the diagnosis. If the other examinations are normal, the concentration test may be repeated, and rather often, in our experience, it is normal. When there has been no other detectable change in the patient's condition which might explain a sudden improvement in concentrating ability, it has been our inclination to suspect that the first test was incorrectly performed, and the suspicion is usually directed toward the patient's fluid intake during the period of presumed fluid deprivation.

We have seen such variability in specific gravity more often than might be expected from inaccurate reading or calibration of the urinometer, variation in the degree of dehydration, other changes in the patient's condition which might affect concentrating ability, or the assumed incidence of unreliable conduct during the test. Since patients taking special diets seemed to show the greatest variability, experiments were conducted to assess the effects of diet on concentrating ability and to improve our knowledge of some of the measures of urine concentration. The character and content of urinary solute were varied by alteration of protein and salt intake.

Experimental Procedure

Young men were selected for study who had no historical or physical evidence of renal disease and who had normal urinalysis, blood urea nitrogen concentration, and phenolsulfonphthalein excretion. Throughout the study they remained on a metabolic ward where their intake, output and activity

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were precisely known, and the ambient temperature and humidity were essentially constant.

An overnight dehydration test was conducted after the subjects had ingested a liquid test diet for three days. The composition of each diet is given in table 1. All four diets were similar in their content of calories and water. These diets were intended to represent variations which might be expected in hospitalized patients, and none is remarkably high or low in any constituent.

From 7:00 p.m. on the third day of the test diet until the specimens were collected the next morning, the subjects took nothing by mouth and remained in bed. The first morning urine was discarded, and the next two specimens were saved for analysis. At the time the first urine was collected, blood

TABLE 1

Character and Composition of Diets
(Content/Kg. Body Weight)

Diet	Na mEq.	K mEq.	Protein Gm.	Osmolar Load* mOs
A Normal	2.0	1.0	1.0	11.7
B Low salt Low protein	0.2	0.7	0.5	4.7
C High protein Low salt	0.2	1.0	2.0	13.8
D High salt Low protein	4.0	0.7	0.5	12.3

* Calculated as 5.7 mOsm. per gram of dietary protein.

was drawn and Pitressin was administered. After the second specimen was collected, the subjects started on the second diet, and after three days the concentration tests were repeated. The same procedure was followed for the third and fourth diets. All urine was voided without catheterization.

Thirty-six concentration tests were performed on nine subjects. Seven subjects completed the test procedure with all four diets; two subjects completed two dietary periods, and two subjects repeated the procedure with Diets C and D while receiving one-half the usual water allowance.

METHODS

Total solid content of urine (grams per 100 gm. of urine) was determined gravimetrically after cryochemical lyophilization for 24 hours. The refractometric analyses were made with a Bausch and Lomb dipping refractometer at 17.5° C. For convenience, the instrumental increment of urine as compared to water (in arbitrary units, R) is used rather than conversion to refractive index from the manufacturer's tables. Osmolar concentration was estimated from freezing point depression using a Fiske osmometer. Specific gravity ($D_{15°}^{20°}$) was obtained with a Westphal balance and empirically converted to $D_{15°}^{15°}$ by multiplying by the measured value of

1.0016. Details of these methods have been described previously.[3] Nitrogen, creatinine, sodium and potassium were determined by the methods usually employed in this laboratory.[4]

Results

Of the two urine specimens analyzed during each test, the one containing the highest concentration of total solids was selected for presentation. In

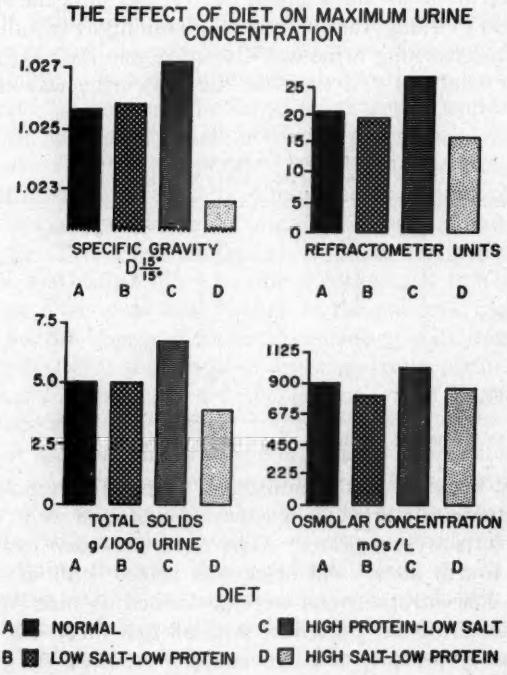

Fig. 1. The maximal urine concentration depicted is the average obtained over all studies. As refractometry and total solids were not performed in each instance the population of reference is not identical.

the few instances where total solids were not determined, the specimen with the highest refractometer reading was selected.

Figure 1 shows the mean of the maximal concentration achieved following each of the four diets. By each of the four measures of concentration, the highest values followed Diet C (high-protein, low-salt). The lowest values generally occurred following Diet D (low-protein, high-salt).

The effects on urine concentration produced by Diets C and D, which differed only in the per cent of total solute contributed by protein and salt, are compared in figure 2. The average concentration was higher on the

high-protein diet. One subject (designated by a +) failed to show an increase in concentration as measured by specific gravity and osmolar concentration. Total solids were not determined, but the refractometer reading was higher.

Figure 3 shows the ratios of urea and salt in the urine, the volume, and the creatinine clearance during these two test periods. The osmolar contribution of salt was calculated as twice the sum of the observed sodium and

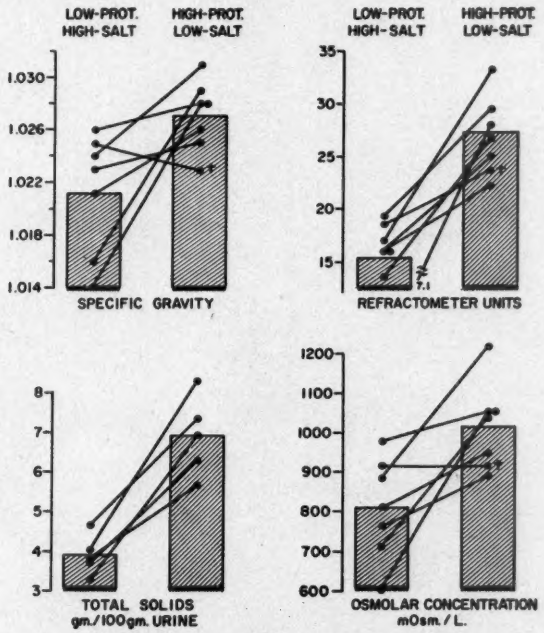

FIG. 2. Comparison of two diets in the same subjects. With the high-protein, low-salt diet, six of the seven subjects concentrated better by all four measures. One subject, designated by the +, had increased refractometric reading but failed to increase osmolar concentration and had lower specific gravity. Total solids were not determined in this subject.

potassium concentrations, to allow for anions; the osmolar contribution of urea was calculated from the observed total nitrogen concentration as if all the nitrogen existed as urea; the sum of salt and urea, so derived, was taken as 100% of the urinary solute. This calculation is shown only to illustrate the direct variation of urinary and dietary solute, but it also correlates well with the urinary osmolar concentration as determined by freezing point depression.

The mean minute-volume of urine was much smaller after the high protein diet, but at such low rates of flow no quantitative estimates could be made of differences in an individual patient after he took one or another diet. Similarly, changes in creatinine clearance in individual patients could not be judged by analysis of specimens voided spontaneously during dehydration. There was no significant difference between the mean values for creatinine clearance obtained following the two diets.

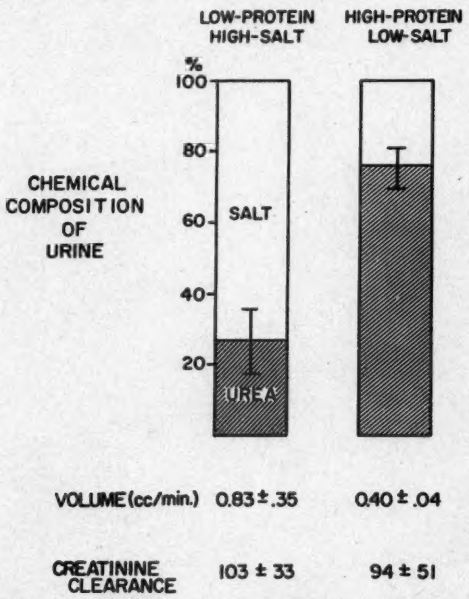

FIG. 3. The ratios of urea and salt in the urine, calculated on an osmolar basis, after diets C and D. See text for method of calculation.

To determine whether the superiority of the high-protein diet could be negated by increasing the degree of dehydration, Diets C and D were again fed for three days each to each of two subjects, but the fluid allowance was reduced from 2,000 c.c. to 1,000 c.c. daily. As shown in figure 4, increasing the degree of dehydration increased the urinary concentration following both diets, but the superiority of the high protein diet was still apparent.

DISCUSSION

These experiments demonstrate that the ability of normal subjects to concentrate their urine under the stimulus of overnight dehydration is enhanced when the antecedent diet is high in protein. Epstein et al.[5] have made similar observations. This property of dietary protein may be the basis for some of the variability of concentrating ability seen in patients tested serially,

since hospitalized patients, particularly those with chronic renal disease and those on special diets, often do not take adequate protein unless it is prescribed. Measures which insure a high intake of protein should enable a patient to attain his maximal concentration for the degree of dehydration on the first test.

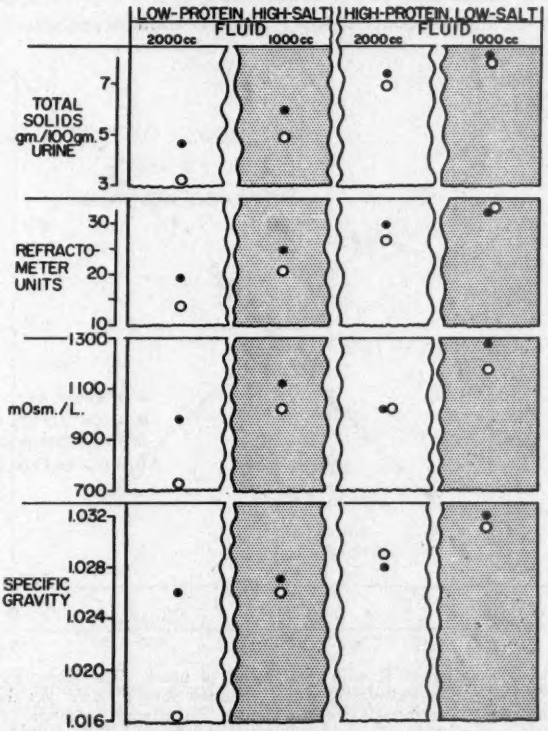

FIG. 4. The effect of antecedent dehydration. The shaded areas represent chronic dehydration induced by restricting total fluids to 1,000 c.c. for the three days preceding each test. Two patients are shown. In each the effect of diet is evident despite the increased urine concentration induced by increasing the dehydration stimulus.

It is always difficult to evaluate a concentration test which is on the borderline between normal and abnormal, but in some situations the decision is crucial. In our military practice, perhaps more than in civilian practice, an accurate knowledge of a patient's concentrating ability may be a factor in his survival. An example which is not uncommon is the soldier who some months ago had acute renal disease and now has questionable hyposthenuria. He has no symptoms or abnormal physical findings, and there are no other laboratory abnormalities. If it is a fact that he has a defect in concentrating ability, he is unfit for general duty, because to place him on general duty

status is to certify that he is physically eligible for sudden transfer to the desert or the Arctic. In these environments, in particular, the water supply may be limited and rationed according to the usual requirements of the average healthy man. A soldier with hyposthenuria might go into collapse on a water ration which would be adequate for one whose kidneys could conserve water normally. The military physician therefore has a serious responsibility to assess concentrating ability with accuracy. In addition,

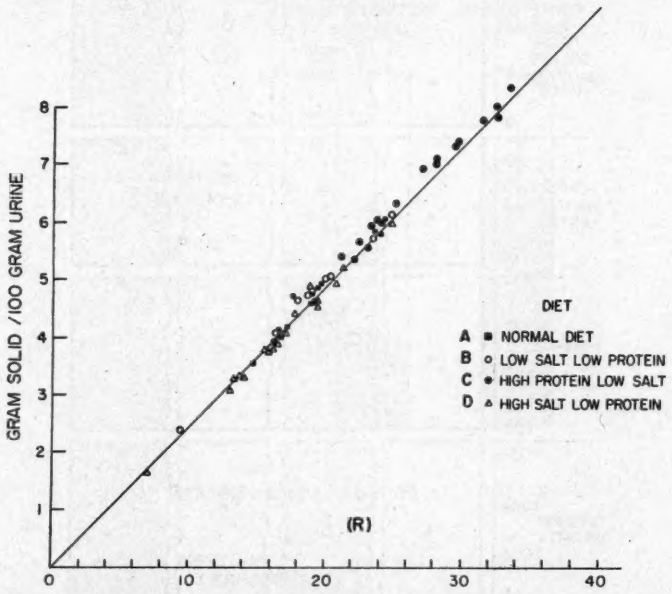

FIG. 5. The correlation of R with total solids of urine. The slope, K, of the best fit line, *fixed at the origin,* was calculated by the equation $K = Y^2/XY$. As the population of points is drawn from an artificially limited sample, no attempt is made to define general regression equations applicable to randomly collected human urine. Certain of these relationships have already been determined on a large series of urines.[3]

he needs this information to protect the patient's legal right to compensation for any disabling residual of a disease incurred in line of duty. Perhaps there are counterparts in civilian medical practice.

In the present experiments four methods were used to measure the concentration of urine. Whether one or another method is chosen as the standard of reference depends upon the focal point of interest. A chemist interested primarily in the physical properties of urine, rather than the capability of the kidney, might consider the weight of the dried solids as the ultimate criterion of concentration. The procedure of drying frozen urine under reduced pressure and weighing the solids directly is too slow and tedious to be practical in a hospital, even if it were otherwise desirable. The

same information can be obtained more quickly from the refractometric reading, which correlates rather precisely with the content of solids (figure 5). However, this information is of little value to the clinician, even if the procedures are available. The weight of the solute gives no indication of the chemical identity of the compounds excreted. The refractometer reflects the weight accurately, but it is relatively indifferent to the type of the solute predominant in urine (figure 6).

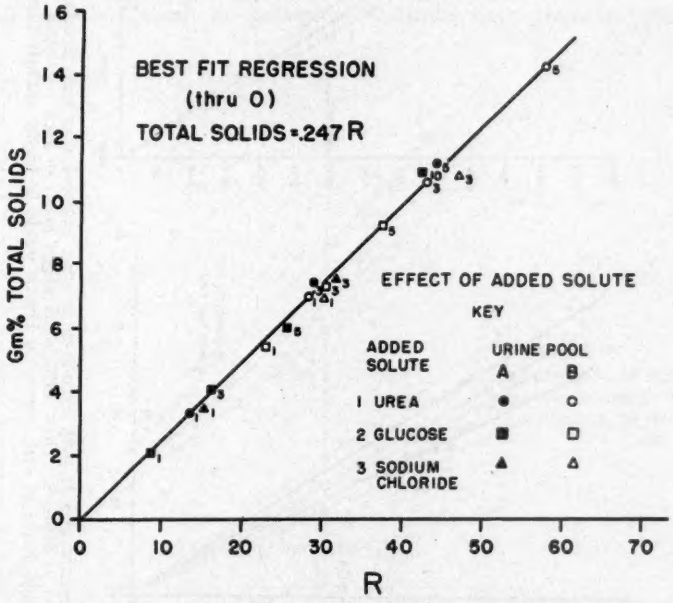

FIG. 6. The addition of urea, glucose or sodium chloride to human urine did not distort the linear relationship of R to total solids. The numerals (● 1) illustrate the amount of each substance (grams) added to 100 c.c. of urine.

As a measure of the concentrating power of the kidney, the number of particles in a given volume of urine has more physiologic significance than does the weight. The number of particles in urine can be estimated from a comparison of the freezing point of urine with that of standard solutions of known osmolar concentrations. As shown in figures 7 A and B, neither the weight of the solute nor the refractometric analysis correlates well with the osmolar concentration, unless the type of solute is predetermined by diet or chemical analysis. A better correlation is seen in figure 7 C, in which specific gravity is plotted against osmolarity. This, in a sense, is contradictory, because specific gravity is a measure of weight, not of particulate concentration, and might be expected to correlate better with the content of total solids, but it does not (figure 8).

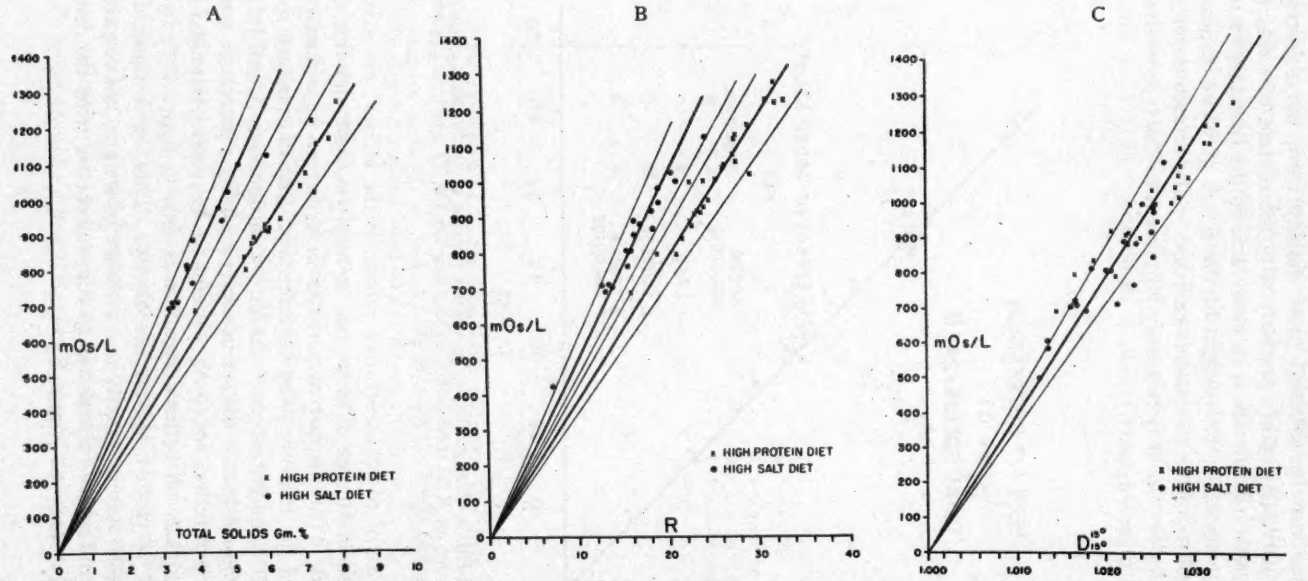

FIG. 7. The correlation of total solids, R, and specific gravity with osmolarity in urine excreted after high-protein or high-salt diets. The best fit lines (heavy lines) are calculated as described in figure 5. The± 10% limits (light lines) of each regression line are shown for comparison. In the absence of overlap between the ± 10% limits of each regression line, it would be highly unlikely that the differences between diets depend on chance alone.

This apparent discrepancy is a result of the different physical properties of the urinary solutes. Specific gravity is related to the weight of the final solution, not just the weight of the solutes. Some molecules incorporate water more intimately than others, and a greater weight of water is contained in the same volume of final solution. One hundred cubic centimeters of urine containing 6 gm. of solute have a higher specific gravity if the principal solute is salt than if it is urea,[6] because the salty urine contains more water. It also contains a greater number of osmols, because one molecule of the salt, mostly sodium or potassium chloride, may dissociate into two

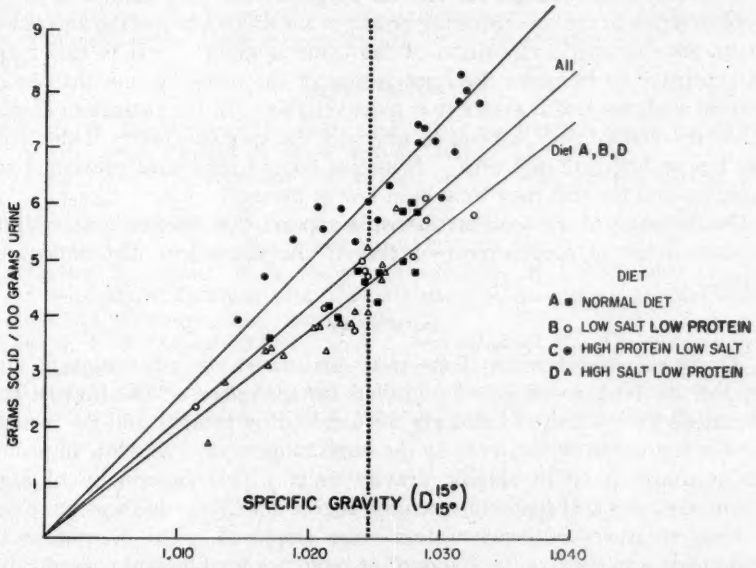

FIG. 8. The poor correlation of specific gravity with total solid content when the diet is uncontrolled. A specific gravity of 1.024 (dotted line) represents about 4 gm. of solute if the diet is high in salt, but about 6 gm. if the diet is high in protein. Several urines from each study are plotted, including those not maximally concentrated.

particles, as sodium and chloride, each of which contributes to osmolarity. In urine, as in other solutions, the dissociation of the salt is not complete, and the contribution of other compounds to osmolarity varies with their proportions and properties. It is fortuitous that the greater osmolarity of urine rich in salt is comparable in degree with the greater specific gravity, and so specific gravity is a better estimate of osmolarity than it is a measure of weight of solute.

The physical result is that a specific gravity of 1.024 represents about 4 gm.% of solute in a urine which is rich in salt, and about 6 gm.% of solute in a urine which is rich in urea (figure 8), but the osmolar concentrations are about the same (figure 7 C). The physiologic result, however, is that

a specific gravity of 1.024 represents normal concentration if the urine is rich in salt, but may signify a defect in concentrating ability if the urine is rich in urea. This apparently contradictory statement is true because the normal kidney has the capacity to excrete greater concentrations of urea than of salt, by whatever measurement (figure 2).

It is fortunate as well as interesting that the specific gravity measurement should correlate so well with osmolarity. The clinical urinometer is available everywhere, and when properly calibrated and used this venerable device provides a quick and inexpensive estimate of specific gravity. The values are accurate enough for clinical purposes, but they cannot be interpreted in terms of the concentrating power of the kidney unless the antecedent diet or the chemical composition of the urine is known.[6] It is easier and less expensive to influence the composition of the urine by diet than to do chemical analyses, and it probably is more reliable. In the absence of dietary control it could be very difficult to interpret the specific gravity if the urine were low in both salt and urea. Nonrenal factors may have prevented salt excretion, and the diet may have been low in protein.

On the basis of these observations, it appears that specific gravity is an adequate index of concentrating ability if the antecedent diet is high in protein.

Summary

Thirty-six concentration tests were performed on nine subjects after they had received one of four liquid diets for three days. The highest concentrations were achieved following the diet high in protein, and the increase over the concentration achieved by the same subjects on a diet low in protein was as much as 0.014 specific gravity units. This superiority of high-protein diets was still apparent when the degree of dehydration was increased.

Four measures of concentration were employed. The weight of the dried solids was used as the standard of reference for physical concentration of urine. In this measurement the refractometer proved to be superior to osmometry or specific gravity measurement. However, osmolar concentration is a more physiologic measurement of the concentrating power of the kidney, and in this measurement specific gravity proved to be superior to total solids or refractometry.

Regardless of which measurement is used, it cannot be interpreted unless it is known whether the principal solute in the urine is salt or urea. The simplest measurement is specific gravity, and a practical way to cause the urine to be rich in urea is to give a high-protein diet before the concentration test is performed.

Summario in Interlingua

Trenta-sex tests de concentration esseva executate pro nove subjectos post que illes habeva recipite un de quatro dietas liquide durante un periodo de tres dies. Le plus alte concentrationes esseva effectuate post un dieta ric in proteina. Le superiori-

tate de iste concentrationes in comparation con illos effectuate post un dieta a basse contento de proteina variava pro subjectos individual usque al maximo de 0,014 unitates de gravitate specific. Le superioritate de dietas ric in proteina remaneva apparente quando le grado de dishydratation esseva augmentate.

Quatro mesuras de concentration esseva empleate. Le peso del solidos desiccate esseva usate como standard de referentia pro le concentration physic del urina. In iste genere de mesuration le refractometro se provava superior al osmometria e al determination del gravitate specific. Tamen, le concentration osmolar es un mesura plus physiologic del potentia concentratori del ren, e in iste procedura le gravitate specific se provava superior a solidos total o a refractometria.

Non importa qual mesuration es usate, illo non pote esser interpretate si on ignora si le soluto principal in le urina es sal o urea. Le mesuration le plus simple es illo del gravitate specific, e un methodo practic a render le urina ric in urea es administrar un dieta ric in proteina ante le execution del test de concentration.

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VARIANTS OF KARTAGENER'S SYNDROME IN THE SAME FAMILY*

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KARTAGENER described the triad of situs inversus, bronchiectasis and chronic sinusitis in 1933.[1] Isolated instances of the syndrome had previously been reported by Siewert [2] and by Gunther.[3] Recently, emphasis has been laid on other associated errors of development, notably those of nasal sinuses other than absent, or small, frontal sinuses.[4, 5] Individuals with dextrocardia without situs inversus, but associated with bronchiectasis and sinusitis, have been generally accepted as valid cases of this syndrome.[6] Bergstrom et al.[7] reviewed the literature through 1949 and collected 80 cases, adding two of their own. They described a family in which two siblings presented Kartagener's syndrome, two had bronchiectasis and sinusitis without dextrocardia, and two were normal. The father had only chronic sinusitis, and the mother was well. They were unable to find a previous report of Kartagener's triad in one sibling and bronchiectasis with sinusitis in another sibling. The family to be presented has similar features, which are felt to represent incomplete forms of this syndrome.

CASE REPORTS

Case 1. The youngest daughter, age 5, was hospitalized in April 1955, for bronchopneumonia and was found to have a complete situs inversus. Past history revealed that she had had a chronic cough since the age of two. This had become progressively more productive during the last year. During the first 12 months of life she had had numerous upper respiratory infections, and the following year, repeated tracheobronchitis. From this time on she has continued to have a productive cough and numerous "heavy colds." In addition, she had repeated tonsillitis associated with her respiratory infections. The recognition of this associated symptom-complex prompted further evaluation of this child and her family.

Physical examination revealed a well developed, apparently healthy five year old girl with a complete situs inversus. She had marked hypertrophy of the tonsillar and adenoid tissue. The chest was clear to auscultation and percussion. The heart was normal except for the dextrocardia position. The tuberculin skin test was negative. Electrocardiogram revealed a true dextrocardia. The electrophoretic pattern of the plasma proteins was normal. Roentgenography showed absence of the frontal sinuses, with retardation of development of the remaining paranasal sinuses. The ethmoid and left maxillary sinuses were clouded. Serial chest x-rays showed a constant infiltrate in the left lower lobe adjacent to the cardiac border. Bronchoscopy in January, 1956, revealed a diffuse chronic bronchitis, but bronchograms failed to demonstrate atelectasis or bronchiectasis. An adenotonsillectomy was per-

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formed following these studies. This improved the nasal airway, and there has been a noticeable lessening of the cough. Further episodes of acute bronchitis will be promptly treated with antibiotics.

Case 2. The father, age 40, had a history of chronic sinusitis that had first manifested itself at 12 years of age. Except for this he has been in good health. Roentgenograms of the paranasal sinuses and chest were normal.

Case 3. The mother, age 39, has always been in good health. There were no abnormalities of the chest and sinus x-ray films. There was no history of chronic pulmonary disease in the last two generations of the families of either parent.

Case 4. The eldest daughter, age 14, presented a history of constant productive cough that was first noted at about two years of age. As an infant her history had been uneventful until 20 months of age, at which time she developed recurrent tonsillitis. This necessitated adenotonsillectomy at two years of age. Her cough persisted, becoming more productive of mucopurulent bronchial secretions. She has had 10 bouts of pneumonia, during which time the cough always worsened. Bronchograms at six years of age were said to be normal. Several nasal polyps were removed a year and a half ago.

Physical examination showed a well nourished, apparently healthy 14 year old girl. Her nasal passageways were partially occluded bilaterally, due to polyp formation. Chest auscultation revealed occasional rhonchi over the right middle lobe area. The patient's tuberculin test was negative; the electrocardiogram was normal. The electrophoretic pattern of the plasma proteins was normal. In September, 1955, a roentgenogram revealed an extensive infiltrate of the right middle lobe. The heart appeared to be normal. Bronchograms in January, 1956, revealed a tubular bronchiectasis localized to the right middle lobe. Paranasal sinus films revealed an absence of development of the frontal sinuses, with small sphenoid and ethmoid sinuses. The maxillary antra showed considerable cloudiness. A polypectomy with bilateral maxillary antral drainage was performed in January, 1956. A right middle lobectomy was performed in March, 1956. There was no chronic cough or sputum production on reëvaluation four months postoperatively.

Case 5. The eldest son, age 13, has had sinusitis since the age of five. He has had no pulmonary symptoms. Physical examination was essentially normal, except for nasal congestion and purulent postnasal discharge. Roentgenograms revealed marked antral membrane thickening and, to some extent, thickening of all membranes of the sinuses. The heart and lungs were radiographically normal.

Case 6. The youngest son, age 8, has had symptoms consistent with sinusitis for the last two years. He has had no pulmonary symptoms. Physical examination was normal except for nasal congestion. Roentgenograms showed slight membrane thickening in the antra. The heart and lungs were normal.

Discussion

The clinical course of Kartagener's syndrome is characterized by nasal discharge, frequent colds, and chronic bronchitis in early infancy. At least 90% of these individuals manifest symptoms prior to age 14.[7] There is usually a history of repeated episodes of pneumonia. These symptoms progress to nasal catarrh, anosmia, headache and chronic cough productive of foul smelling sputum with occasional hemoptysis. Asthma, emphysema, bronchiectasis, pulmonary osteoarthropathy and cor pulmonale are eventual complications.

The lesions present in the nose and sinuses of these patients are varied,

There may be mild or severe sinusitis, hypoplasia or agenesis of the sinuses, and nasal polyposis. Bronchograms will usually reveal partial atelectasis and tubular bronchiectasis, more often bilateral and involving the lower lobes, lingula, and right middle lobe to a variable degree. The incidence of bronchiectasis occurring in persons with situs inversus or dextrocardia varies from 12 to 23%, as contrasted to 0.03 to 0.5% of the general hospital and clinical population.[8, 9] Situs inversus itself occurs in approximately one of 6,000 to 8,000 persons.[3, 6, 7, 12-14] Probable cases of this syndrome have been reported with agenesis of the sinuses without evidence of sinusitis,[8] as well as of sinusitis without evidence of bronchiectasis.[15] Churchill [15] referred to two children whom he observed to have situs inversus and agenesis of the sinuses without definite evidence of bronchiectasis. Both had profuse nasal discharge and expectoration of large amounts of mucous secretions. They had had the benefit of favorable climate and chemotherapy, and bronchiectasis was not yet apparent. The features present in the five year old daughter are very similar. She had situs inversus, sinusitis, underdeveloped paranasal sinuses, and chronic bronchitis with left lower lobe fibrosis. It is felt that she will eventually develop bronchiectasis unless prophylactic therapy is successful. Furthermore, as evidenced by the family described by Bergstrom et al.[7] as well as the one described by the writers, there can be incomplete forms, with bronchiectasis and sinusitis without dextrocardia. The 14 year old daughter had agenesis of the frontal sinuses, underdeveloped paranasal sinuses, sinusitis, nasal polyposis, and bronchiectasis without dextrocardia. Also, two of the siblings in the family had sinusitis only.

The exact nature of the respiratory defect or the manner of inheritance is not completely clear. Published reports indicate that the bronchiectasis associated with this syndrome is tubular rather than cystic, and the microscopic findings are those of the acquired type. Bronchiectasis in the stillborn with dextrocardia has not been reported. Also, a significant number of individuals with the triad have not had symptoms of bronchiectasis until late childhood or adulthood. In the cases presented, the 14 year old daughter did not have bronchiectasis when a bronchogram was performed at the age of six, and the five year old daughter has not as yet developed bronchiectasis. The evidence therefore seems overwhelming that the sinusitis and bronchiectasis are acquired in the sense that they develop after birth.

In the family presented it would appear that there is a respiratory tissue defect of a variable extent. It has been postulated that there is an elastic tissue defect,[12] or possibly an altered secretory activity of the respiratory tissue, which renders these individuals susceptible to infection. It is unlikely that there is a general or metabolic defect which renders such individuals susceptible to infection. Churchill's theory [15] that there is altered secretory activity of the respiratory tissue would readily explain the selectivity of the site of infection. This aspect must await detailed autopsy evaluation of the

newborn in every instance of dextrocardia, for once superimposed infection occurs, the picture is that of inflammation and degeneration.

The familial tendency indicates an antenatal influence, which may be the result of genetic factors, or environmental influences, acting prior to or during the earliest stages of cell division. Adams and Churchill have shown that two types of people are affected by transposition of the viscera [9]—normal persons known as mutants, and those in whom the abnormality is associated with other congenital defects, known as monsters. These other defects include congenital heart disease, hydrocephalus, imperforate anus, cleft palate, accessory digits and hypospadias. An occasional case of Kartagener's triad is reported with other congenital defects, including congenital heart disease, hypospadias and duplicated kidney. They classify Kartagener's syndrome as a minor monstrosity. If there were a genetic factor, the triad should be seen in more than one generation. This has not been described. The horizontal distribution suggests an environmental factor active at the start of embryonic life. This would explain the abnormalities in the family reported here—that is, they are actually minor monstrosities. However, Cockayne [16] concluded that a single recessive autosomal gene was responsible for the inheritance of the situs inversus, and that this gene was harmful in that it also permitted a tendency to bronchiectasis. Torgersen [10] disagreed, feeling that the tendency for bronchiectasis was inherited, and that this might or might not be accompanied by situs inversus as a result of the interreaction of several genes. Thus the exact reasons for the familial tendency are not completely clear and must await further follow-up of known families through several generations, as well as the evaluation of new cases.

In the child, though local chronic inflammatory changes of the lymphoid tissue or allergic problems are the commonest causes of chronic respiratory symptoms, one must consider rarer causes, such as congenital heart disease with increased pulmonary blood flow, abnormalities of the great vessels with an aortic ring or anomalous retro-esophageal artery, Kartagener's syndrome, agammaglobulinemia, and chronic cystic disease of the pancreas. The latter two diseases commonly have associated chronic pulmonary symptoms. The absence of male sex-linked inheritance and multiple system infections, along with the presence of normal gamma globulin with abundant adenoid and tonsillar tissue in the siblings of this family, rules out agammaglobulinemia. The normal nutritional status, the presence of normal stools and as yet well localized pulmonary involvement do not suggest chronic cystic disease of the pancreas.

In view of the high incidence of bronchiectasis in patients with situs inversus, all children with dextroposition of the viscera, with frequent upper respiratory tract infections, should be evaluated for bronchiectasis and sinus infections so that proper prophylactic therapy may be instituted as early as

possible before marked damage occurs. As exemplified by this family, siblings should be thoroughly screened for similar abnormalities.

Summary

A family is presented in which one sibling had situs inversus, sinusitis, underdeveloped paranasal sinuses, chronic bronchitis and left lower lobe fibrosis. Another sibling had sinusitis, agenesis of the frontal sinuses, underdevelopment of the remaining sinuses, nasal polyposis, and bronchiectasis without dextroposition of the viscera, while two siblings had sinusitis only. It appears that the bronchiectasis and sinusitis are acquired, though there is a definite antenatal influence. The exact nature of the respiratory defect or the manner of inheritance is not clear on reviewing the literature. In the families described by Bergstrom et al.[7] and the writers, it is apparent that this syndrome can occur in various combinations within the same family. The importance of early recognition and prompt therapy is reëmphasized.

Summario in Interlingua

Le syndrome de Kartagener ha essite describite como un triade de sito inverse, bronchiectasis, e sinusitis chronic. Variantes de isto ha essite recognoscite como casos valide del mesme syndrome. Pote occurrer absentia del sinuses frontal e hypodisveloppamento del altere sinuses. Polyposis nasal con hyperplasia adenoide e tonsillar es usualmente presente. Dextrocardia sin sito inverse es commun. Depost le introduction del antibioticos, individuos de etate pauco avantiate pote experientiar plure episodios de pneumonia, bronchitis chronic, e—in le curso del tempore—fibrosis pulmonar sin signos demonstrabile de bronchiectasis.

Es presentate un familia que exhibi formas incomplete de iste syndrome. Un del fraternos habeva sito inverse, sinusitis, hypodisveloppamento del sinuses paranasal, bronchitis chronic, e fibrosis pulmonar sinistro-inferior. Un secunde fraterno habeva sinusitis, agenese del sinuses frontal, hypodisveloppamento del altere sinuses, polyposis nasal, e bronchiectasis sin dextroposition del visceres. Un tertie e un quarte fraterno habeva solmente sinusitis.

Il pare que le bronchiectasis e le sinusitis es acquirite, ben que il existe un definite influentia antenatal. Tamen, le exacte natura del defecto respiratori o le maniera del hereditage non se clarifica per un revista del litteratura. In le familias describite per Bergstrom e alteres e in illo hic reportate, il es clar que iste syndrome pote occurrer in varie combinationes in le mesme familia. Es sublineate le importantia de un prompte recognition e de un prompte institution del therapia.

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GALLOP RHYTHM*

By JAMES V. WARREN, *Durham, N. C.*, JAMES J. LEONARD, *Washington, D. C.*, and ARNOLD M. WEISSLER, *Durham, N. C.*

To many, gallop rhythm presents no problems. It is simply an extra heart sound in diastole heard in patients with actual or incipient congestive heart failure, and is of dire prognostic significance. Unfortunately, there is considerable evidence that the problem is not so simple. On careful study one finds similar diastolic heart sounds in normal persons. Gallop sounds are found in different parts of the diastolic phase, and the prognostic implications differ. With the current interest in more accurate cardiac diagnosis because of the increasing scope of cardiac surgery, the time would appear to be ripe for a reassessment of this problem. We must consider, therefore, what is a gallop, why does it occur, and what are its diagnostic and prognostic implications.

When the physician becomes interested in gallop rhythm he is immediately struck by the frequency with which he hears these sounds, as compared with his past experience. The ability of the human ear to hear sounds differs in various ranges of the frequency spectrum. The sounds of middle frequency range are most readily heard, whereas those of very high frequency or very low frequency are heard only when their physical intensity is quite high. (A schematic representation of these findings by Fletcher and Munson [1] is an almost certain illustration in any manual on high fidelity phonographic technics.) It has been pointed out that in order to be heard, a low-pitched gallop sound must be many millions of times louder in a physical sense than a high-pitched aortic diastolic murmur.[2] This, in addition to the inherently more noticeable nature of high frequency sounds over low frequency ones, accounts for much of the difficulty that physicians encounter in hearing gallop rhythm. Only the loudest and most obvious gallops will be noted if the physician does not pay particular attention to the diastolic phase of the cardiac cycle and evaluate it with great care. In addition, it has recently been emphasized that the level of noise in the examining room is an important consideration.[3] A gallop sound may be heard much more readily on examining the patient in a truly quiet room than on a noisy hospital ward.

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If one amplifies and records the heart sounds phonocardiographically, vibrations are seen even more frequently than sounds are heard by the human ear without amplification. In addition, the vibrations may be accurately timed with respect to the normal heart sounds, electrocardiogram, or to a vascular pulse wave. In certain aspects, therefore, phonocardiography represents the ultimate in technics for the study of the sounds under discussion in this paper. One may, based on these findings, build an entirely defensible concept of heart sounds and gallop rhythm. The practicability of such a schema may be questioned because, in practice, most physicians use the ear unaided by amplification. Our enthusiasm for phonocardiographic detection is tempered by such considerations, so that it is utilized as an analytic tool rather than as a basic means of setting up our schema for practical clinical use.

There is overwhelming evidence that the simple unitarian concept of gallop rhythm is inadequate. Careful studies by many investigators have revealed that there are several distinctly different sounds that may be heard during the diastolic phase.* Differences in terminology have caused some confusion, but the evidence indicates that several sounds are involved. First, there is the early diastolic (protodiastolic or ventricular) gallop sound, which is generally accepted as the pathologic counterpart of the normal third heart sound. Second, there is a presystolic (auricular, or atrial) gallop sound, which occurs shortly before the first sound, and which is probably the most common of all diastolic gallop sounds when careful auscultation is carried out. An apparently specific sound is heard in patients with mitral stenosis occurring early in diastole, which is called an opening snap of the mitral valve. Another diastolic sound is heard in patients with pericardial disorders, often called a pericardial knock. At times a split first sound or a split second sound may occur, so that one component may be mistaken for a diastolic extra sound and not a part of the normal two heart sounds.

For many years it has been recognized that, in addition to the classic two sounds of each cardiac cycle, a third and occasionally a fourth sound may be audible. Cardiologists have recognized that these sounds are apt to be heard in young individuals, particularly children and young adults with a slender, asthenic habitus, and that exercise will frequently bring them out when they are not audible at rest. The third heart sound is a low-pitched, short vibration heard at about the end of the first third of diastole, when the heart rate is within normal limits. Its occurrence can be correlated with the end of the period of rapid ventricular filling that occurs in early diastole. Dock and his colleagues have recently evaluated the evidence regarding this sound, and have concluded that it is produced by temporary reclosure of the auriculoventricular valves.[4] In a small group of individuals a fourth heart sound is heard, following shortly after contraction of the atrium. It is perhaps of similar valvular origin, this time related to the ventricular filling

* The so-called systolic gallop rhythm will not be considered in this discussion.

produced by atrial contraction. It appears to be the normal counterpart of the atrial (presystolic) gallop sound. It is important to recognize that these sounds are essentially the same sounds that will later be discussed as gallop sounds, but that on making their appearance in different company they are called by different names.

Ventricular Gallop

The ventricular gallop sound, often called a protodiastolic or rapid filling sound, usually occurs at about the end of the first third of diastole. It is a low-pitched, short sound, best heard near the apex or between that point and the pulmonic area. It is often enhanced by those maneuvers which increase the murmur of mitral stenosis, such as having the patient turn on the left side, and following a brief period of exercise. It is important to note that this is a sound of quite low frequency and, as in the murmur of mitral stenosis, it is heard best with the bell of the stethoscope, with care taken not to press too firmly upon the skin. Tension caused by the stethoscope makes the skin act as a diaphragm and filters out the low frequency sound.

If one carefully observes or records the palpable pulsations at the apex, it is possible to notice a very strong apical heave at the time of the ventricular gallop sound (figure 1). It has been our experience that this is far more pronounced in the gallop sound than it is in its normal counterpart, the third heart sound, and may be a useful means of differentiation. The vibrations are of such low frequency that often they can be better felt than heard. Studies by means of the ballistocardiogram and the electrokymograph likewise demonstrate energetic ventricular impulses simultaneous with these sounds. Correlative studies with intracardiac pressure phenomena reveal that this sound occurs at the end of the period of rapid ventricular filling. Since this is usually at about the end of the first third of diastole, we associate this sound with that time—hence the name, protodiastolic. It must be remembered, however, that with rapid heart rates and under other special circumstances, the sound may assume a position that is either midway in diastole or even in the presystolic zone.

There is ample clinical evidence to support the fact that the sound described as a ventricular gallop appears in patients with incipient or actual congestive heart failure. It must be remembered that a similar sound (third heart sound) may be heard on occasion in normal individuals—hence a diastolic sound does not *necessarily* mean heart failure even when heard in the patient with heart disease. It has been noted that this sound is not heard in association with tight mitral stenosis, presumably because the valve defect prevents rapid ventricular filling. The occasional sounds that are heard in the early diastolic phase of such patients may be related to events in the right ventricle.

What causes the ventricular gallop sound? Many possibilities have been suggested. Some evidence indicates that it is of valvular origin. The

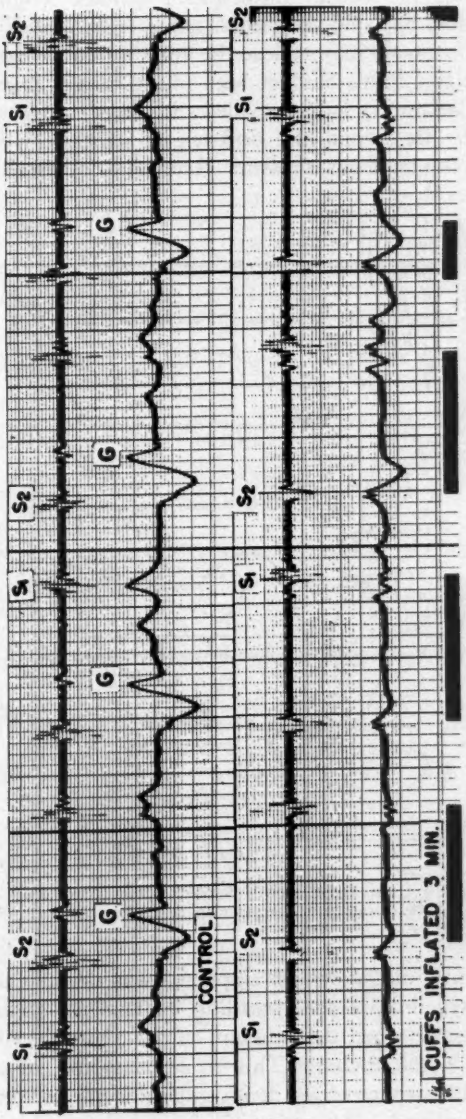

FIG. 1. Simultaneous phonocardiogram and apex cardiogram in a patient with ventricular gallop (G). Note the feeble atrial (presystolic) gallop. After three minutes of peripheral pooling the ventricular gallop disappears and the associated apical impulse is diminished.

illustrations almost 50 years old by Yandell Henderson illustrate a widely held concept regarding the mechanism of gallop sounds [5] (figure 2). The pressure wave produced by rapid ventricular filling reflects off the ventricular wall, tenses, and on occasion may reclose the auriculoventricular valve. Although widely held, this thesis has not been unequivocally proved. Recent observations in our laboratory have provided additional evidence. Catheters were introduced into the atrium and ventricle of patients with right-sided gallop sounds and simultaneous pressure recordings obtained (figure 3).

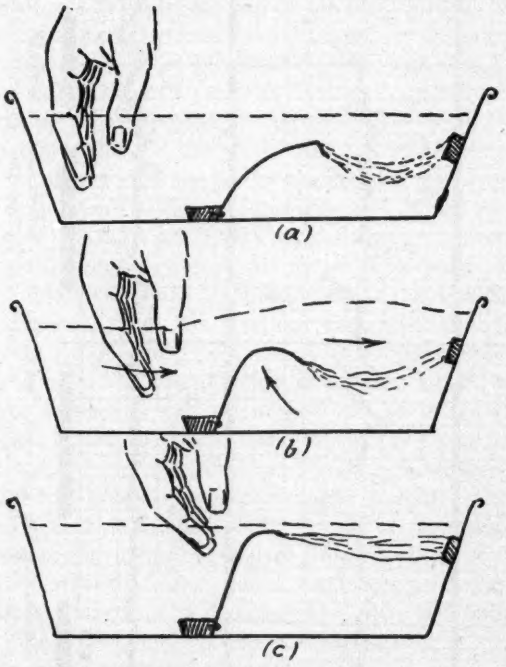

FIG. 2. An illustration from Henderson [5] demonstrating a possible mechanism for gallop sound production. Reproduced with the permission of the publishers of *Heart* (Clinical Science).

The frequency response of the system employed was deemed adequate, and care was taken to synchronize the recording instruments accurately. The sound occurs in diastole when the pressure in the ventricle rises over and above that existent in the atrium. This situation would, of course, cause retensing and actual reclosure of the atrioventricular valves, consistent with the thesis already outlined. Alterations in intracavitary pressure, such as can readily be produced by peripheral pooling of blood by the application of tourniquets about the extremities, can alter the gallop sound, even causing it to disappear [6] (figure 1). Similar results may occur when the patient

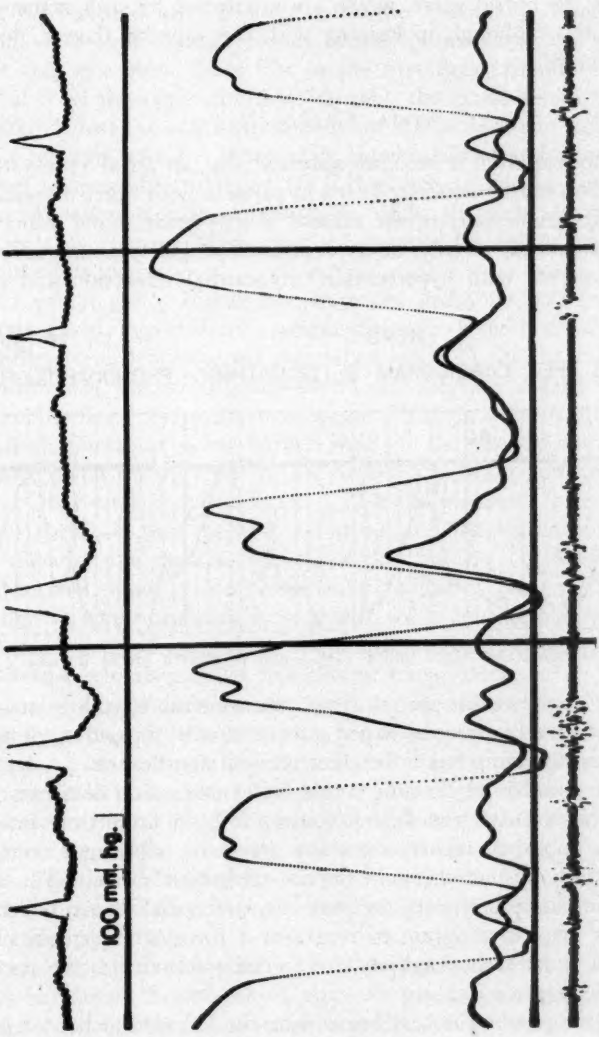

FIG. 3. Simultaneous right atrial and ventricular pressure tracing in a patient with cor pulmonale and loud gallop sound (summation). Note occurrence of sound only at the time of transient pressure reversal during ventricular diastole.

stands up. This has proved to be practically useful in attempting to differentiate the ventricular gallop from other sound phenomena, such as the opening snap of the mitral valve, which are unaffected by such maneuvers. These observations, although in keeping with the valvular theory, do not offer definitive proof.

Atrial Gallop

On careful auscultation it becomes apparent that an atrial (presystolic) sound is the gallop most frequently heard in patients with heart disease. It is the pathologic counterpart of the normal fourth heart sound which, although well recognized, is only rarely heard. The gallop sound is heard frequently in patients with hypertension, myocardial infarction and heart

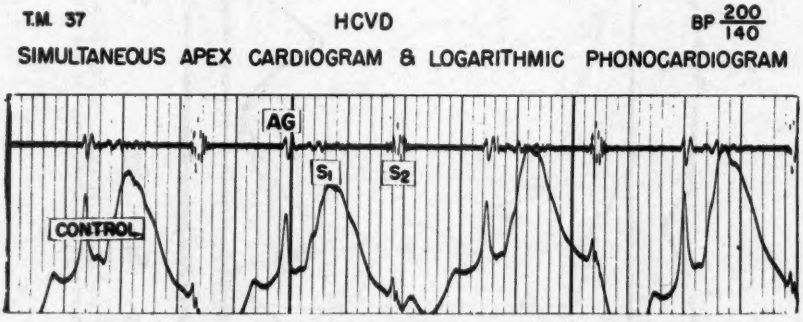

Fig. 4. Demonstrates atrial gallop (AG) and prominent apical thrust.

block of either complete or partial type. In contrast to the ventricular gallop, the atrial sound is frequently not associated with impending or actual heart failure, and therefore has a different clinical significance.

It should be pointed out that the sound under discussion does not occur simultaneously with atrial systole, but follows it by a finite time interval. Although many published reports show low frequency vibrations occurring with atrial systole, most of them are in the subaudible range. The atrial gallop occurs simultaneously with the peak of a precordial thrust, which can be identified by apex cardiogram to represent a forceful movement of the ventricular wall, apparently resulting from atrial ejection into the partially filled ventricle [7] (figure 4).

The atrial gallop sound is best heard near the left sternal border in the fifth interspace, although at times it is loudest at the apex. Because of its low frequency, it too is visualized and palpated much more readily than it is heard. Evans,[8] in emphasizing this point, has recommended that the sound be elicited by applying the ear directly to the chest wall. Such a maneuver obviates the stethoscopic filtration of the low frequency sounds and results in the apical thrust against the ear, reinforcing the sound.

Under what circumstances does an atrial gallop appear? Analysis in patients with complete heart block demonstrates that these sounds occur about 0.21 second after inscription of the P wave.[9] With normal sinus rhythm, ventricular systole usually begins by this time, and an atrial sound either does not occur or is lost in the first heart sound. When the PR interval is at the upper limits of normal, the atrial sound may occur immediately before the first heart sound, but the unaided ear cannot distinguish it as a separate sound. If the time between atrial and ventricular systole becomes abnormally prolonged (first degree heart block), an audibly separate atrial sound appears. In addition, under these circumstances the audibility of the extra sound is enhanced because the following first sound is diminished in intensity.

Presystolic gallop sounds are, however, probably most frequently heard in patients with hypertensive vascular disease. Experimental studies in this laboratory have demonstrated that when blood in the extremities is pooled by tourniquets, the atrial gallop sound will migrate toward the first sound and become fused within it or disappear.[10] Such experiments indicate that the atrial vibrations occur earlier than in the normal individual. They therefore stand out in front of the first heart sound and are audible as a separate, low-pitched gallop sound. In some instances there is evidence of another factor, in that the first sound may be delayed more than the usual time following the electrical systole of the ventricle (prolonged Q-1 time).

The atrial sound is also occasionally audible in acute myocardial infarction, and in some instances may persist for a considerable period of time. As far as we are aware, there is no information available regarding any specialized mechanism under this clinical circumstance.

Atrial gallop sounds emanating from the right side of the heart are frequently present in patients with pulmonary hypertension, regardless of its cause. These sounds may have a striking respiratory variability, often being particularly loud on inspiration. The right-sided atrial sounds are best heard in the region of the xiphoid, and, in contrast to other situations, may be present even when the patient is sitting or standing up. These sounds, like their left-sided counterparts, may occur in the absence of congestive failure, and may have the same prognostic implications as left-sided atrial gallop rhythm.

A circumstance most conducive to the appearance of an atrial gallop is that of left bundle branch block, since its presence is frequently associated with first degree heart block, and since the bundle branch block results in the first heart sound being delayed in onset, faint in intensity and long in duration.[11] In addition, such a conduction defect is frequently the result of the changes of long-standing arterial hypertension or myocardial infarction (figure 5).

Atrial gallop is presystolic only insofar as atrial contraction is usually presystolic. As the PR interval becomes increasingly prolonged, it may

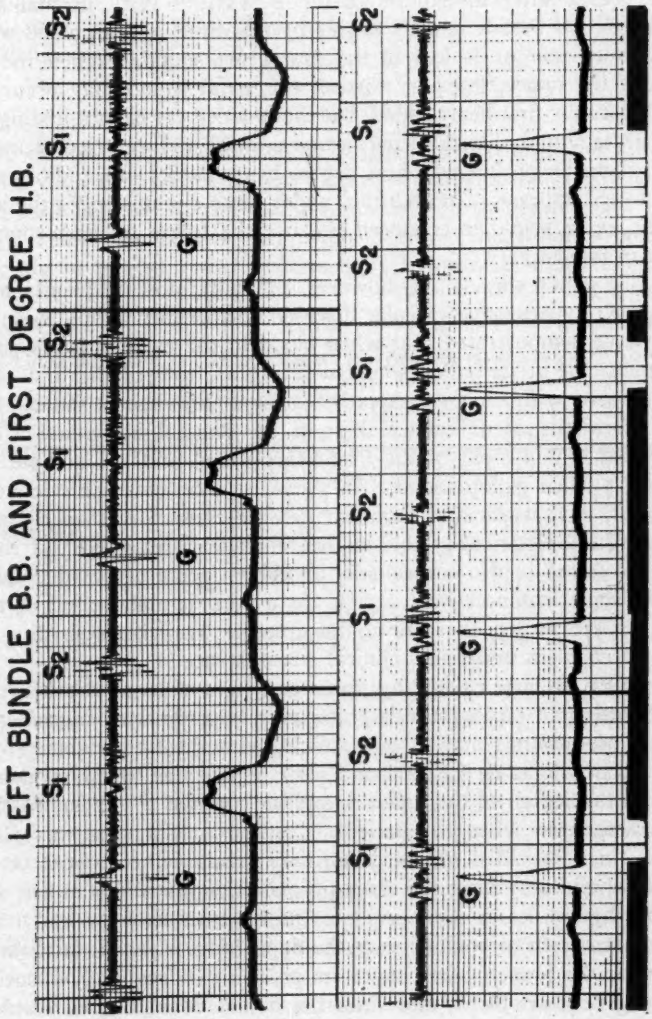

FIG. 5. Simultaneous phonocardiogram and electrocardiogram in a patient with intermittent heart block. Note changes in atrial gallop (G) and first heart sound (S_1).

be seen not in presystole but in mid-diastole, or if the heart rate is fast, even in protodiastole. If such a rapid heart rate is slowed by carotid sinus pressure, a constant relationship to the first sound identifies it as of atrial origin.

Two other triple rhythms may be confused with the atrial sound. Differentiation of splitting of the first sound is generally not difficult. Such sounds are usually of equal pitch and amplitude, occurring close together and varying with respiration, being more widely split on expiration. A far more difficult triple rhythm to differentiate is an early ejection sound in the face of a faint first heart sound. The first sound is followed by a sharp, high-pitched sound of striking intensity. One may mistake the ejection sound for the first sound, and the faint first sound is labeled an atrial gallop. Such a sequence is common in severe aortic insufficiency. The first sound is frequently faint because of prolongation of the PR interval. One can usually avoid this pitfall if one is aware of the fact that atrial gallop is unusual in severe aortic insufficiency, in spite of the relatively common occurrence of first degree heart block.[9, 12] Both an ejection sound and atrial gallop can be present in coarctation of the aorta or pulmonary hypertension (figure 6).

The "Pericardial Knock," or Diastolic Sound of Constrictive Pericarditis

Since its description by Potain,[13] this sound has been recognized as a valuable diagnostic adjunct in the identification of pericardial disease. It usually occurs about 0.08 to 0.12 second after the beginning of the second sound. This time relationship makes it obvious that the sound may at times be confused with the opening snap of mitral stenosis or a ventricular gallop. To add to the possible confusion in those patients with constrictive pericarditis in whom the sound occurs early, it is even higher pitched, similar to the opening snap, and when it occurs later it is likely to have more low frequency components, similar to a ventricular gallop sound. In general, the pericardial sound occurs earlier than does the gallop, is of a higher frequency, has a striking respiratory component, is transmitted widely, and may even exceed the other heart sounds in intensity.

Analysis of ventricular filling in patients with constrictive pericarditis presenting this sound has been very informative. The ballistocardiogram, the electrokymogram and the apex cardiogram, as well as the intraventricular pressure curve, all bear a striking similarity. The common denominator is the steep filling curve which comes to an abrupt halt early in diastole. Thereafter, volume displacement and pressure traces suddenly become flat. This configuration is a caricature of the filling wave seen in ventricular gallop rhythm. It is at the junction of the two phases of the diastolic cycle that the extra sound occurs. An interesting correlation between the steepness of the wave slope and the loudness, pitch and time of

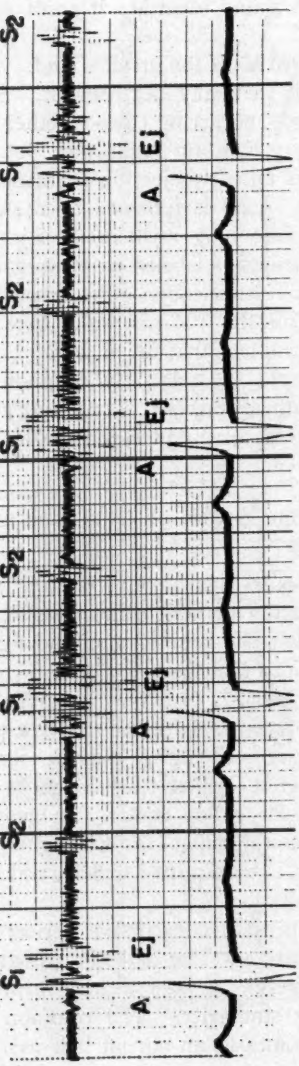

FIG. 6 (*above*). Demonstrates atrial gallop (A) and ejection sound (Ej) in a patient with coarctation of the aorta.

FIG. 7 (*below*). Simultaneous phonocardiogram and apex cardiogram in a patient with mitral stenosis and opening snap (O.S.). Note the absence of an associated diastolic impulse and the gradual upward slope of the apex cardiogram during diastole.

onset of the sound has been reported.[15] When the filling wave has a more gradual curve, this sound occurs later and is of lower frequency. After the pericardium has been stripped, the sound may remain, but now occurring later, in the time interval of a ventricular gallop. This and other evidence indicates that we may be dealing with only a modified ventricular gallop and not a truly different phenomenon.

Opening Snap of Mitral Stenosis

This sound occurs soon (0.04 to 0.12 second) after the onset of the second sound. It is short and higher in pitch than the other gallop sounds, and is heard best in the third or fourth interspace to the left of the sternum (figure 7). There is an inverse relationship between its time of onset and the pressure gradients across the mitral valve. It is important not to confuse an opening snap with a gallop. An opening snap may be the only auscultatory sign of mitral stenosis, but more usually it is associated with a sharp first sound, and a diastolic rumble. Apparently an opening snap and a gallop in the same ventricle are mutually exclusive. This becomes plausible when one looks at the filling curve of the left ventricle in mitral stenosis. The rise is gradual, and there is no change in the slope. Thus the striking change between early and late filling seen when gallop rhythm is present does not occur, and a gallop sound is not produced. It must be remembered that severe heart failure due to mitral stenosis may result in a *right* ventricular gallop sound in the face of a *left* ventricular opening snap.

When the opening snap occurs relatively late (about 0.12 second) after the second sound, a problem in differentiation from ventricular gallop exists. Apex cardiograms may aid in differentiation by the type of filling curve and its time relation to the extra sound (figure 7). In addition, although there is often a diminution or disappearance of a ventricular gallop sound after five minutes of pooling of blood by means of tourniquets, the application of such cuffs has no effect on the opening snap. Thus, if blood pooling changes the sound, it is indicative of a gallop sound and not of an opening snap.

Splitting of the Second Heart Sound

In young people there may be a relative delay in closure of the pulmonic valve in relation to the aortic valve.[2] This causes slight splitting of the second heart sound as it is heard in the pulmonic area. Even with wide splitting of this sound, it is not often confused with a gallop because the sounds are of the same pitch. The widening and narrowing of the split with inspiration and expiration aid in identification (figure 8). The most widely split second sounds, that is, those of right bundle branch block and intra-atrial septal defect, however, may not have this phasic variation. These sounds can still be differentiated from gallop rhythm, since they are heard well at the base and with the patient sitting up, whereas the gallop sound is

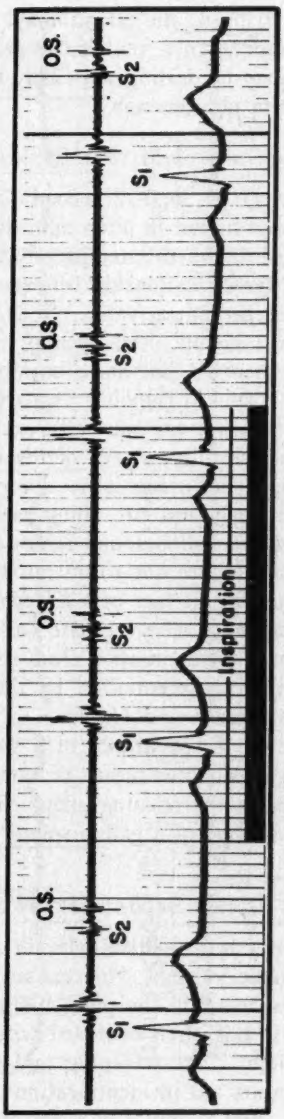

FIG. 8. Demonstrates phasic respiratory variation in the splitting of the second sound, while the opening snap remains unaltered.

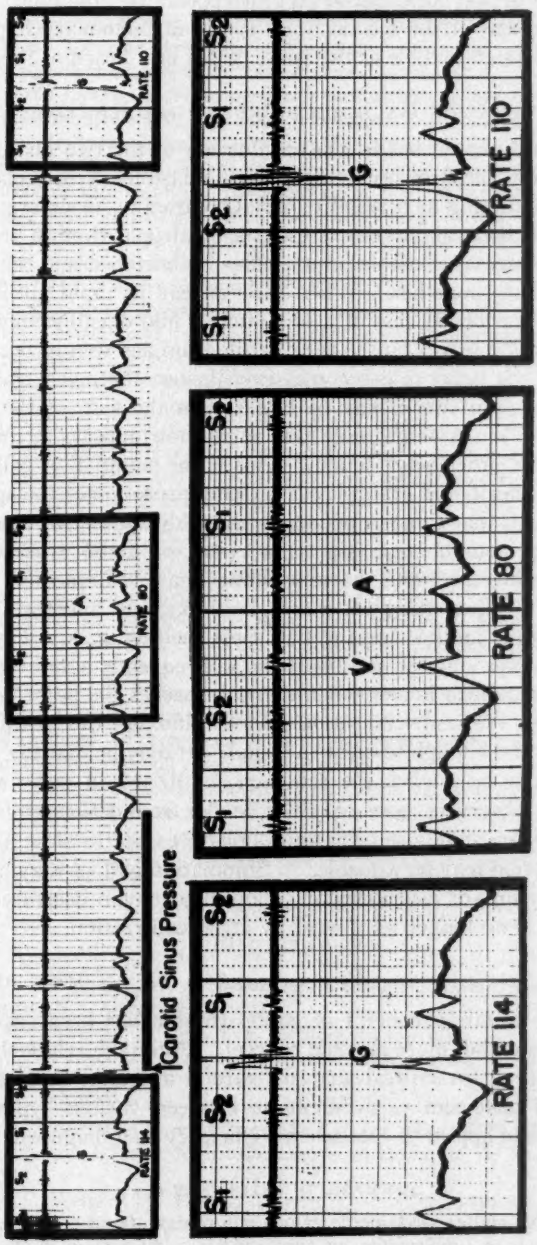

FIG. 9. The use of carotid sinus pressure to demonstrate summation gallop. Note that there is summation of the apical impulses as well as of the gallop sounds.

more obvious near the apex and usually disappears on standing. The loud pulmonic component of the second heart sound in pulmonary hypertension, for instance, although audible at the apex, is still best heard at the base.

Summation Gallop and Quadruple Rhythm

Gallop sounds are related to the termination of the two phases of rapid ventricular filling, the first occurring in protodiastole (ventricular gallop), and the latter occurring as a result of atrial contraction in presystole (atrial gallop). When both sounds are present a quadruple rhythm results. As the heart rate increases, diastole in particular is shortened and the two extra sounds come closer together. When they appear in rapid succession, the impression is occasionally one of a low-pitched mid-diastolic murmur. At this point the gallop waves on the apex cardiogram are seen to occur in close succession. If the heart rate becomes even faster, the apical gallop waves fuse and the resultant wave may be larger than the sum of the two components (figure 9). A single very loud sound now appears in mid-diastole, often louder than either heart sound. This is the summation gallop so well described by Wolferth and Margolies.[16] Upon inspection of the apex cardiogram, one realizes that this is not merely the addition of two sounds, but a new and louder sound, occurring as a result of atrial systolic ejection, actually reinforcing the rapid diastolic filling phase. Immediate variations come to mind. When the two waves reinforce one another, a diastolic sound may become audible for the first time, neither gallop wave of itself being sufficient to produce an audible sound. Frequently a ventricular gallop suddenly becomes much louder when the rate reaches the point where atrial systole reinforces the ventricular gallop wave, although this atrial wave was of itself not forceful enough to create a sound. It may be that the impression that gallops occur only when the rate exceeds 100 is an outgrowth of the fact that some observers note only the louder summation gallops, which require a fast rate. The use of carotid sinus pressure to slow a rapid rate during examination may be valuable.[17] Summation gallops may be split into a quadruple rhythm, or a ventricular gallop may remain decreased in intensity, because it is no longer reinforced by atrial contraction.

Conclusions

The simple unitarian concept of gallop rhythm has been superseded by a more complicated but more rational concept. Although relatively elaborate means are required for critical analysis, careful auscultation at the bedside will enable the physician to differentiate between various types of gallop sounds, and would appear to increase his efficiency as a diagnostician.

Summario in Interlingua

In le opinion de multes, rhythmo de galopo non representa un problema. Pro illes, rhythmo de galopo es simplemente un sono cardiac additional in le diastole que es

audite in patientes con presente o incipiente congestive insufficientia cardiac, e su signification prognostic es triste. Infelicemente it ha forte indicationes que le question es minus simple. Le bruit de galopo es incontrate in diverse portiones del phase diastolic, e su signification prognostic es complexe.

In le presente reporto nos considera per consequente le questiones: Que es un galopo? Proque occurre illo? Que es su importantia diagnostic e prognostic?

Frequentemente bruits de galopo non es audite per le medico proque lor altor de tono es basse de maniera que illos es mal percipite per le aure human mesmo si lor intensitate physic es considerabile. In multe casos il es plus facile sentir le galopo tactilemente que audir lo acusticamente. Le normal cyclo cardiac contine duo sonos diastolic que es audibile in certe individuos. Illos ha essite designate como le tertie e le quarte sono cardiac, e illos es relationate, le un al rapide replenation ventricular al initio del diastole e le altere al contraction atrial.

Le sono ventricular (protodiastolic o de replenation ventricular rapide) es un sono de basse altor que es audite al initio del diastole e que es frequentemente associate con insufficientia cardiac ver o potential. Illo es le correspondentia pathologic al tertie sono cardiac. Le atrial (pre-systolic) bruit de galopo es audite in le diastole ante le prime sono cardiac. Illo es simile al quarte sono cardiac in un altere milieu. Illo non es specificamente associate con congestive insufficientia cardiac. Illo es frequentemente audite in patientes con hypertensive morbo cardiac o con infarcimento myocardial e in situationes con prolongate conduction atrioventricular. Le clic de apertura del valvula mitral es audite in patientes con stenosis mitral. Illo es un acute sono protodiastolic que occurre un pauco plus proxime al secunde sono que le sono de galopo ventricular. In casos de morbo pericardial, specialmente in pericarditis constrictive, un forte e prominente sono protodiastolic es audite un pauco ante le tempore characteristic del galopo ventricular traditional sed post le clic de apertura. Es formulate le opinion que il se tracta hic de un sono del typo de galopo ventricular que es audite plus precocemente a causa del alterate circumstantias physic. In caso de alte rapiditate cardiac, le phenomenos que produce le galopo ventricular e le galopo atrial pote combinar se e producer le si-appellate galopo de summation. Isto es un sono specialmente forte que occurre proxime al centro del diastole in le presentia de alte frequentia cardiac. In certe casos le fission del normal sonos cardiac pote resultar in confusion e misinterpretation como bruit de galopo.

Le simple e unitari concepto del rhythmo de galopo ha essite reimplaciate per un concepto plus complexe sed plus rational. Ben que relativemente complexe medios es requirite pro le analyse critic, le meticulose auscultation al lecto del patiente permitte al medico differentiar inter le varie typos de bruit de galopo e augmentar su efficacia como diagnostico.

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MURMURS IN CHILDREN: A CLINICAL AND GRAPHIC STUDY IN 500 CHILDREN OF SCHOOL AGE *

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A century ago, auscultation of the heart led to recognition of adventitious sounds and murmurs which were explained as the result of heart disease. Medical opinion has differed widely since then, and three different thoughts have been entertained: (1) a murmur is always significant of abnormal conditions of the cardiovascular system; (2) no importance should be attached to murmurs; or (3) a murmur may or may not be significant, depending upon the area of audibility, loudness, duration, pitch, timbre and radiation.

Controversies have been even more numerous in regard to children, who seem to present murmurs much more frequently than do adults.

It is the opinion of the authors that, while a murmur may have have no clinical significance, *there is no murmur without cause.* Recognition of the latter is frequently a challenge for the physician. Even now, at times we must acknowledge our inability to explain certain murmurs.

The Systolic Murmur: The occurrence of systolic murmurs without definite evidence of heart disease has been recognized since Laënnec. However, Levine [1] states: "Systolic murmurs do occur but are not common in normal individuals. The louder ones are always associated with some form of cardiovascular disease. All systolic murmurs deserve consideration. Many such murmurs, although frequently regarded as 'benign' because the individuals feel well and have no symptoms of cardiac insufficiency, are due to organic changes or indicate potentialities for the subsequent development of stenosis of the mitral or aortic valves, hypertension, and subacute bacterial endocarditis. Others are truly benign in the sense that no deleterious effects result, even after an indefinite period."

It should be stated that certain patients, after an attack of rheumatic fever, present a systolic murmur caused by deformity of a valve, which then

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persists unchanged for 20 or 30 years with no evidence of cardiac enlargement or failure. Therefore, the three criteria—no failure, no enlargement, no change of the murmur—are still inadequate for excluding a valvular deformity of minor or moderate severity.

Functional Murmurs or Innocent Murmurs? The term "functional" murmur was created about a century ago to separate murmurs not caused by obvious valvular deformity from the others. The most common instances were systolic murmurs of the apex or base of the heart, encountered in severe anemia, pregnancy, or congestive failure, which subsequently disappeared.

In the last 30 years some of the mechanisms causing "functional" murmurs have been clarified and can be summarized as follows:

1. *Severe tachycardia* may cause a moderately loud systolic murmur. The mechanism is probably multiple (acceleration of flow, incomplete valvular closure, etc.).

2. *Severe anemia* usually causes a loud apical and midprecordial systolic murmur. The mechanism is probably multiple, including dilatation of the tricuspid and mitral rings (relative tricuspid and mitral insufficiency). Anemia may also cause a loud apical and midprecordial diastolic murmur. This seems to be due to dilatation of the ventricles greater than that of the auriculo-ventricular ostia (relative tricuspid and mitral stenosis) and to more rapid blood flow.

3. Conditions associated with *increased blood volume* (pregnancy), *greater rapidity or quantity of systemic or sectional blood flow* (hyperthyroidism, septal defects), or *dilatation of one of the large arteries* (aortitis, congenital dilatation of the pulmonary artery) frequently present a systolic murmur at the base. The mechanism seems to be a disproportion between a normal ostium and a dilated vessel, and a trigonoidation of the valve (relative aortic or pulmonic stenosis).

Further detailed explanations have been given and can be found in various textbooks of cardiology.

Unfortunately, physicians gradually extended the meaning of the word "functional" to apply to the following murmurs: (a) any murmur of persons with no history of rheumatic fever, and no obvious clinical cardiac enlargement, who are able to develop a normal physical activity without exertional dyspnea; (b) any murmur persisting for many years and unaccompanied by evident modification in loudness or by physical deterioration; (c) any murmur of children or adolescents which is less loud than grade 4.

The reasons for the extremely wide application of the term are obvious, and are frequently based on emotional factors.

It is apparent that the term "functional" murmur tends to change its meaning through abuse and misuse. Created to depict a murmur caused by mechanisms other than permanent valvular deformity, it now tends more and more to become synonymous with "innocent" murmur. This would not be serious if better proofs of such "innocence" were available. Unfortunately,

such proofs frequently are not sought for or are non-existent. Moreover, psychologic and social elements have become so utterly mixed with the term that it has lost its original meaning and would best be abolished.

The American Heart Association has suggested the term "innocent murmur." This is a better term than "functional murmur." Unfortunately, it has a limited value because it is actually based on a complex interpretation and has a negative meaning: an innocent murmur is a murmur which is not going to be associated with any serious cardiac disease. The future developments are simply surmised.

A revised terminology of murmurs was suggested by White, Adams and Craib [3] as follows:

I. *Physiologic murmurs*
- (A) Intracardiac or intravascular
- (B) Extracardiac
  - (a) cardiopulmonary
  - (b) pericardial

II. *Pathologic murmurs*
- (A) Due to structural valvular disease
- (B) Due to congenital defects
- (C) Due to dilatation of ventricles, aorta or pulmonary artery from
  - (a) cardiovascular disease
  - (b) other diseases
- (D) Due to pericarditis

It should be noted that "pathologic murmurs" would include some murmurs commonly called "functional" because they occur with normal valves, as observed by Sodeman.[4] In regard to recognition as to whether a murmur is "physiologic" or "pathologic," again a complex process of reasoning is involved, and a mistake is possible unless the clinical course is followed for many years or autopsy findings are available.

Even the disappearance of a murmur is not sufficient proof that it is a physiologic murmur. Bland, Jones and White [41] collected several cases of rheumatic heart disease where the murmur disappeared in spite of minor valvular lesions. In one case this was proved by autopsy.

The Systolic Murmur of Children and Adolescents: If a systolic murmur is not rare in apparently normal adults, it is far more common in children and adolescents. The relative frequency noted on clinical auscultation by various researchers is summarized in table 1.

Painstaking attention has been devoted to a possible clinical differentiation between *harmless or innocent systolic murmurs* and *significant systolic murmurs* of children or young people. The data collected from medical literature in regard to "innocent" murmurs can be summarized as follows.

Area. The murmur is heard more often over the pulmonic area [3, 10, 16, 18] but may be heard at the apex,[3, 10, 16, 18] within the apex,[16] or over the entire precordium.[10, 16] Friedman et al.[28] found 39% of murmurs in children to be pulmonic, while Messeloff [29] found *22%* of them in this area.

Type of murmur. The murmur heard over the pulmonic area has been defined as *groaning,*[18] *twanging-string,*[19, 20, 21] *vibratory,*[17] *musical* [22] or *soft and blowing.*[4, 14]

Loudness. The murmur may vary from grade 1 to grade 3, seldom more.

TABLE 1

Clinical Studies of Systolic Murmurs in Children and Adolescents

Year	Authors	Age Group	No. of Subjects	Percentage with Murmurs	Remarks
1938	Siemsen	Infants	105	25	Percentage increased with subsequent examinations. Occasional musical murmurs or loud murmurs. Usually apical.
1940	Rauh	1st–8th grade	710	20	
1941	Schwartzman	12–19	5,541	43.9	(In addition to 2.42% with organic heart disease.) Murmurs in 83.6% after exertion.
1942	Bock	Medical freshmen	526	18.8	
1943	Contratto	Medical freshmen	2,856	12.3	In 4% the murmur was very loud and remained undiagnosed. In 7%, the term "functional" was used.
1947	Evans	Young adults	330 (selected)	Not stated	Phonocardiography also employed. Murmurs often midsystolic, occasionally late-systolic.
1948	Epstein	1–7	251	50	
1948	Quinn	7th–8th grade	4,370	35.2	
1951	Gardner and Keith	School age	1,146	61.3	
1952	Maresh, Dodge and Lichty	6th grade	11,236	36.4	6.7 had rheumatic heart disease. 2.7 had congenital heart disease.
1956	Lynxweiler and Donahue	Not stated (Pediatric Clinic)	1,706	36	Children referred to Pediatric Cardiac Clinic for study; follow-up for 6 years (2.2% of this group later proved to have congenital heart disease).

Duration. The murmur is usually short.[23]

Recumbency. The murmur is usually louder in the recumbent position, and may be inaudible when sitting.[4, 10, 16, 18, 23]

Respiration. The murmur is usually louder at the end of expiration, but occasionally may be louder at the end of inspiration.

Exertion. Exertion usually increases the loudness of the murmur. However, it may cause it to disappear.[23]

Transmission. The murmur is claimed to be limited.[23] If so, murmurs heard over most of the precordium should be classified as originating in more than one valvular orifice.

It should be noted that the above criteria, even though based upon the experience of numerous clinicians, are by no means safe. They would have

a much greater value if the subjects had been followed through life, or if autopsy data were available. Moreover, they are not basically different from data which can be observed in certain organic murmurs. For example, organic murmurs originating in the tricuspid or pulmonic valve are increased by recumbency, whereas most organic murmurs are increased by exertion.

A majority of adults with valvular disease of obvious rheumatic etiology have no knowledge of ever having suffered from rheumatic fever during childhood or adolescence. This creates a serious problem, and one cannot help but wonder whether those adults with valvular lesions had murmurs during adolescence.

Graphic Studies of Systolic Murmurs in Children: The first study was made in 1933 by Bass et al.[22] By the use of several filters it was ascertained that the "functional" murmur contained only *high-pitched* vibrations in 86% of 64 cases. It was also noted that the murmur occupied either the first half or the major part of ventricular systole. McKee [23] in 1938 recorded phonocardiograms of normal children and detected a faint, *low frequency* systolic murmur in 90%. Mannheimer [24] in 1940 made a systematic study of the phonocardiogram of children by means of different filters. Systolic murmurs of comparatively *low frequency* were recorded quite commonly: in 50% of the cases for a range of 100 to 250 cycles and in 72% of the cases for a range of 50 to 175 cycles (135 children were studied in all). Murmurs below 1 mm. of amplitude were discounted.

More recently Evans [11] considered it to be typical of the systolic pulmonic murmur that it starts in midsystole and is spent before the second sound.

Harris, Friedman and Haub [25] studied 13 children with mitral insufficiency and 30 children with nonblowing systolic apical or precordial murmur (25 of them of a musical type). The musical (or vibratory) murmur was shorter, had regular vibrations, and was separated by a short pause from the first heart sound. The same observation was repeated by Harris and Friedman [26] in a group of 28 children, and by Harris [27] in 40 children. Harris and Needleman [42] then reported graphic studies in "normal" children and in children with rheumatic or congenital heart disease.

On the other hand, graphic studies of Luisada and Magri [30] and Zilli [31] revealed vibratory or musical pulmonic murmurs during the acute stage of rheumatic fever, and their attenuation or disappearance when clinical evidence of "activity" had ceased. A similar observation was made by Jones,[32] who recorded phonocardiograms in 125 children with acute rheumatic fever. He observed that in eight out of 70 presenting a pulmonic systolic murmur, there was a vibratory murmur widely separated from the first sound.

Material and Method

Our study was conducted in 500 children between the ages of four and 17 from four public schools of Greater Chicago. The children were unselected, and were studied in groups by classes. However, to obtain a good

cross-section of the population, the following distribution was obtained:

55 cases from an all-Negro grammar school in a poor section of the city.
45 cases from a Catholic kindergarten in a white neighborhood from families of average income.
320 from a grammar school with a mixed population (about three quarters white) from both high and low income families.
80 from a grammar school in the best residential section of the Greater Chicago area with an all-white population.

Approximately equal numbers of males (49%) and females (51%) were studied. Seventy per cent of the children were white and 29.2% were Negro, while the remainder were Indo-American.

The percentages by ages were as follows:

Age	Percentage
4	0.8
5	0.6
6	4.2
7	9.6
8	24.4
9	14.4
10	10.8
11	9.8
12	8.4
13	3.6
14	7.2
15	1.8
16	4.0
17	0.4

It can be seen that 67.8% of the children were between eight and 12 years of age.

Clinical examination. Each child was examined successively by three cardiologists, who wrote their findings separately. These were then compared and tabulated.

The examination of the child was made in both the supine and the sitting or standing position. In one group of children, special maneuvers were made (rotation or flexion of neck) to determine if the loudness of the murmurs was modified thereby.

The data recorded were: heart sounds (loudness, splitting); murmurs (area, loudness, characteristics, modifications by respiration or position); effect of special maneuvers. In subjects with loud murmurs, the effect of exercise (10 flexions of the legs) was also studied.

Routine technical examination. This consisted of an exploratory electrocardiogram (standard and unipolar limb leads) and phonocardiogram (tracings recorded over the apex, second and third left interspace, second and third right interspace) by both the "stethoscopic" and the "logarithmic" methods.*

* The Sanborn twin-beam was used. This apparatus has a dynamic type of microphone. The change from "stethoscopic" to "logarithmic" recording is made by flipping a switch, thereby changing the characteristics of the electric system.

TABLE 2
Murmurs Heard on Auscultation

Intensity	Grade	Number	Percentages		
			% of Children	% of Murmurs	% of Children after Excluding Faint Murmurs
Loud systolic	3–4	9	1.8	2.4	7.6
Medium systolic	2–3	107	21.4	28.2	90.0
Faint systolic	1	261	52.2	68.8	—
Diastolic	1–2	2	0.4	0.6	1.6
None	—	121	24.2	—	—

Special technical examination. This was done in 87 cases where loud murmurs or electrocardiographic abnormalities led to suspicion of definite heart disease. In these cases the electrocardiogram included six chest leads; phonocardiographic records were taken over four areas, and fluoroscopy of the chest was performed. Subsequent examinations were made at monthly intervals. In 38 of the above cases a hematologic study was also made.

TABLE 3
Distribution of Murmurs by Sexes

Loudness and Phase	Males	Females
Loud systolic	1 = 0.4%	8 = 3.1%
Medium systolic	61 = 24.8%	44 = 18.8%
Faint systolic	128 = 52.2%	135 = 52.9%
Diastolic	—	2 = 0.7%
None	55 = 22.4%	66 = 25.8%
Total	245	255

RESULTS

1. *Clinical finding of murmurs:* Only those murmurs which had been heard by either two out of three observers, or by all three, were taken into consideration. The result is noted in table 2.

2. *The distribution of murmurs by sexes* was approximately even, as shown by table 3, with the exception of loud systolic murmurs.

TABLE 4
Areas of Auscultation of Systolic Murmurs

Loudness	Apex	Midprecordium	Base		
			Aorta	Pulm.	Both
Loud	3	2	—	4	—
Medium	11	29	2	49	14
Faint	38	37	3	168	17
Total	52	68	5	221	31
			257		

TABLE 5

Distribution of Murmurs According to the Different Schools

	Grammar School C	Kindergarten D-P	Grammar School I	Grammar School E-P	Total
Total number of children	56	46	319	79	500
Total number of murmurs	43	31	231	57	362
No. murmurs in phonocardiogram	13	15	88	22	138
Loud	8	2	2	1	13
Medium	4	8	73	17	102
Faint	31	21	156	39	247
School percentage to the total number of murmurs	76.7%	48.4%	72.4%	72.1%	
School percentage (excluding faint murmurs)	21.4%	21.6%	23.5%	22.7%	

3. *The distribution of murmurs by race* was as follows: Of 146 Negro children, 31 (21.2%) had grade 2 or grade 3 murmurs; of 351 white children, 89 (25.3%) had grade 2 or grade 3 murmurs. No significant difference is apparent.

4. *The murmurs were heard at the various areas of auscultation,* as presented in table 4. As shown in this table, the great majority of the murmurs were basal and heard chiefly in the pulmonic area.

5. *Distribution of murmurs in regard to economic status.* This was determined by comparing the percentages of murmurs in the various school groups (table 5). The differences are small, particularly if the averages are made excluding the faint murmurs or those not confirmed by the phonocardiographic records. Therefore, economic status appears to have no bearing.

6. *Relationship of murmurs to height and weight* was studied grossly by establishing an index as follows: The weight in pounds was divided by the height in centimeters. For example, a child 4 feet tall (128 cm.)

TABLE 6

Relationship of Weight-Height to Murmurs (Average Index)

Age	Average Wt./Ht. Ratio in Children Having Murmurs	Average Wt./Ht. Ratio in Children Having No Murmurs
4	0.98	0.90
5	*1.06*	*1.06*
6	1.33	1.29
7	1.19	1.11
8	1.17	0.98
9	*1.25*	*1.25*
10	1.27	1.01
11	1.35	1.22
12	1.70	1.40
13	1.50	1.43
14	2.11	1.85
15	1.87	1.72

weighing 100 pounds would have an index of 0.78. The data are presented in table 6. It can be seen that children with murmurs have an average index which is either equal to or larger than that of children having no murmurs. On the whole, children with murmurs were shorter and squatter than the others.

7. *Changes in the murmurs by changing the position of the child from lying to sitting or in rotating the neck.* Changes of position of the body

TABLE 7

Changes of Murmurs in Passing from the Recumbent to the Sitting Position

	Number	Percentage
Disappeared	26	30.2
Decreased	23	26.9
Unchanged	32	37.1
Increased	5	5.8
Total	86	

were studied in 86 cases with medium or loud murmurs. The results are noted in table 7. In 57.1% the murmur disappeared or decreased, while in 42.9% it increased or persisted unchanged. The effect of bending the head or rotating the neck was studied in 13 children with medium or loud murmurs. The murmur was unchanged by these maneuvers in 10, was increased in two and decreased in one.

TABLE 8

Phonocardiographic Evidence of Murmurs

Magnitude and Phase	No.	Percentage	Percentage of Total No. of Murmurs in Phonocardiogram	Numbers after Excluding Small Murmurs and Diastolic Murmurs
Medium diastolic	1	0.2	0.4	
Large systolic	13	2.6	3.6	114 (22.8)
Medium systolic	101	20.2	27.8	
Small systolic	247	49.4	68.2	385
No murmurs	138	27.6	—	
Total	500			

8. An *electrocardiographic study* was made to determine if any *prolongation of the QT interval* was present in children with loud murmurs. No difference was found when comparison was made with records of other children.

9. *The magnitude of the sound vibrations was further studied in the phonocardiographic tracings* (table 8).

10. *Distribution of intensity of the murmurs in regard to age and sex* in the phonocardiographic tracings is presented in table 9.

11. A *comparison between clinical findings and phonocardiographic data* revealed a difference of evaluation in 25 cases (6.5%), as shown in table 10.

TABLE 9
Distribution of Intensity of the Murmurs in the Phonocardiogram

Age	Loud		Medium		Faint		Total
	Male	Female	Male	Female	Male	Female	
4	—	—	1	—	1	—	2 = 0.4%
5	—	—	1	1	—	1	3 = 0.6%
6	—	2	1	2	4	4	13 = 2.6%
7	1	3	4	6	12	11	37 = 6.8%
8	2	4	14	8	30	28	86 = 17.2%
9	—	—	11	5	19	18	53 = 10.6%
10	—	—	12	6	13	14	45 = 9%
11	—	—	6	2	14	12	34 = 6.8%
12	—	1	3	5	8	13	30 = 6%
13	—	—	3	—	6	6	15 = 3%
14	—	—	1	2	7	8	18 = 3.6%
15	—	—	3	1	3	3	10 = 2%
16	—	—	1	3	5	5	14 = 2.8%
17	—	—	—	—	2	—	2 = 0.4%
Total	3 = 0.6%	10 = 2%	61 = 12.2%	41 = 8.2%	124 = 24.8%	123 = 24.6%	362 = 72.4%

12. Additional details revealed by the phonocardiogram were as follows:

..A third sound was recorded in 248 children (49.6%).
..Both third and fourth sounds were recorded in 60 children (12%).
..A fourth sound was recorded in seven children (1.4%).
..Splitting of P_2 was recorded in 257 children (51.4%), with the following characteristics:

— 0.03 to 0.04" between the two components in 189
— 0.04 to 0.05" between the two components in 65
— 0.05 to 0.06" between the two components in 3

13. The *shape and configuration of the murmur* as revealed by the phonocardiogram were as follows:

..The murmur was *in decrescendo* in 185 cases (51%)
diamond-shaped in 152 cases (42%)
atypical in 25 cases (7%)
..The murmur was *musical* in 197 cases (54.7%)
non musical in 165 cases (45.3%)
..It was widely separated from the first sound in 132 cases (36.5%)
nonseparated from the first sound in 230 cases (64.5%)

TABLE 10
Differences Between Clinical Auscultation and Phonocardiogram

		No.
Murmur more significant in phonocardiogram		4
Murmur less significant in phonocardiogram		6
Murmur excluded by phonocardiogra n	Systolic	14
	Diastolic	1

14. The *location of murmurs,* as revealed by the phonocardiogram, was as follows:

Base only	126	(aorta, 29; pulmonic, 57; both, 40)
Apex only	20	
Apex and base	55	(apex plus aorta, 14; apex plus pulmonic, 31; apex and both pulmonic and aorta, 44)
Midprecordium	117	(midprecordium plus apex, 15; midprecordium plus base, 21)
Entire precordium	81	

15. The *evolution of murmurs,* as revealed by repeated phonocardiograms, was as follows:

Eighty-seven children were reëxamined during the two years of this study.

44 murmurs were unchanged, 34 were decreased, and nine were increased.

16. A *comparison of the phonocardiographic findings and blood examination* was made in 38 children. The survey revealed that:

8 had a color index below 0.9
25 had a color index of 0.9 to 1
7 had a color index of 1 or more

Further data in these selected cases were as follows:

(I) *Children with normal blood* (red blood cells normal, hemoglobin normal). In 30 cases, 13 had a musical, grade 2 or 3, systolic murmur over the pulmonic (or aortic) area.

(II) *Children with abnormal blood* (red blood cells decreased, or hemoglobin decreased). Of 10 cases, four had a musical, grade 2 or 3, systolic murmur over the pulmonic (or aortic) area.

17. *Fluoroscopic studies.* These were done in 40 cases having a grade 2 or 3 murmur. An enlarged and strongly pulsating pulmonary artery was found in 20 cases. Enlarged pulmonary artery and enlarged right ventricle were found in two cases. Enlarged pulmonary artery and enlarged left ventricle were found in one case. Thus, 23 out of 40 cases (75%) had a dilated pulmonary artery.

Discussion

This investigation was started with an open mind. The great frequency of murmurs in children and adolescents has never been adequately explained. A murmur obviously has to be caused by some structural or dynamic mechanism.

Several possibilities have been considered and will be discussed on the basis of the present study.

1. *The systolic murmur of children is inherent in the size and configuration of the cardiovascular system at that early age or is caused by rapid flow or tachycardia.*

These possibilities are denied by three facts:

(a) Not all children have murmurs.
(b) Young children and infants have fewer murmurs than children and adolescents of school age.
(c) Adult animals of a size and weight similar to those of young children have no murmurs.

2. *The development of children is not uniform.* Some children are tall and slender, others squat and short. It might be considered that, at some stage of development, a *disproportion develops between size of the ventricles, opening of the valves, and caliber of the large vessels, particularly the pulmonary artery.*

This possibility was denied by our comparison between murmurs on the one hand, and height and weight of the children on the other: tall, slender children have either the same or a lower incidence of murmurs.

3. The murmur is a systolic pulmonic murmur due to *compression of the pulmonary artery by the chest wall.*[33] This theory is dynamically unlikely. Moreover, it is disproved by the fact that fluoroscopy in the lateral projections fails to show any contact between chest wall and pulmonary artery.

4. *The murmur of children is an extracardiac murmur, probably cardiopulmonary.* This is denied by the fact that apnea in general does not affect the murmur, and that no constant relationship is found between murmur and the phases of respiration.

5. *The murmur is due to anemia.* This was disproved by our study. The frequency of murmurs in children with normal blood is not different from that in moderately anemic children.

6. *The murmur is a vascular murmur originating in the neck.* Changes in the position of the head would cause the murmur to disappear.[34] This was disproved by our study in a great majority of the cases.

7. *The systolic murmur of children has different characteristics from those of organic murmurs.* This again is not true. It was noted that, in the great majority of cases, the murmur persisted in the sitting or standing position. Occasional attenuation was explained by a change in heart rate (orthostatic tachycardia). If the rate was slowed down (inspiratory apnea), the murmur was audible even in the sitting position. Moreover, all murmurs originating in the pulmonic valve become louder in the recumbent position (greater flow to the right heart). Therefore, the only conclusion that can be reached in regard to the characteristics of the murmur is that it behaves like a pulmonic murmur (right heart) and not like a mitral murmur (left heart).

As to the graphic characteristics of the murmur, reference should be made to the study of Jones [32] who recognized frequent pulmonic systolic murmurs in rheumatic children as having the same characteristics (short duration, vibratory type) as those of the "innocent" pulmonic murmur of "normal" children. As these murmurs disappeared with the cessation of the active stage of rheumatic fever, they could not be interpreted as "innocent" murmurs persisting in or accentuated by rheumatic fever.

8. The fact that the murmur is frequently separated from the first sound by a sizable interval is a characteristic typical of all "ejection systolic murmurs," as demonstrated by Leatham.[35] These are produced by turbulence of flow through the aortic or pulmonic valves because of "stenosis, valvular damage, dilatation of the vessel, or increased flow." One of the last two possibilities seems the most probable, and the modification of cardiovascular dynamics is similar to that found in several congenital or acquired diseases of the heart. We actually have found a dilatation of the pulmonary artery in 75% of the children with louder murmurs. However, this does not reveal whether the dilatation is due to increased pulmonic pressure, more rapid pulmonic flow, or intrinsic lesion of the vessel. Studies of Luisada and Magri,[30] Zilli [31] and Jones [32] revealed the frequency of a systolic pulmonic murmur during the active stage of rheumatic fever. This murmur may be explained as due to increased flow (fever), tachycardia (fever), anemia, higher pulmonic pressure (mitral insufficiency due to carditis), or an arteritis of the pulmonary artery due to the rheumatic process. The latter has been actually observed by Gouley and Eiman,[38] von Glahn and Pappenheimer [36] and Kugel and Epstein.[37]

9. If systolic pulmonic murmurs are common in acute rheumatic carditis, and if, moreover, apical and aortic systolic murmurs are present in a certain percentage of "normal" children, can a rheumatic process explain the systolic murmur of children and adolescents?

A common belief was expressed by Maresh and Dodge: [16] "When a murmur of this type occurs with such frequency, it can hardly be considered abnormal." On the other hand, a pathologic process may be extremely frequent without ceasing to be abnormal. One may quote:

(a) Healed pulmonary tuberculous lesions in approximately 85% of the "healthy" adult population;
(b) Syphilis, especially in certain South American or African regions;
(c) Intestinal parasites, especially in the tropical areas;
(d) Coronary arteriosclerosis, especially in this country;
(e) Dental caries or baldness.

None of the above diseases is considered physiologic, even though their incidence is extremely common. Therefore, the problem is to ascertain whether rheumatic fever may have *an extremely discrete form* and may be much more common than is usually thought.

It is obvious that only autopsy findings can give the answer, if made on a large scale.

Before comparing our data on murmurs with objective postmortem data, we should consider whether it is fair to place all murmurs on the same plane. We have come to the conclusion that murmurs heard by only one observer, or inconstant, or grade I, should not be considered. While they might occasionally become significant by becoming louder or harsher, at the moment of observation they were likely to be without any meaning and probably due to a temporary increase of rate.

In 500 unselected postmortem examinations of persons over five years of age, Fassbender [39] found evidence of endocarditis in 307 (61%). On the other hand, only a small minority (5.5%) had severe valvular defects, while the others had minor processes affecting the leaflets, the commissures or the chordae. He finds the greatest increase of valvular lesions between 20 and 25 years of age, and an incidence of valvular lesions of 20% between 11 and 15 years of age. One might question the criteria of Fassbender in admitting rheumatic stigmata (according to certain authors, only the finding of Aschoff nodules gives the certainty that the cardiac lesion is rheumatic). These objections, however, are not valid for the study of Hall and Anderson,[40] who examined 124 hearts and found vascular, perivascular and interstitial lesions, including Aschoff's nodules, in about 20% of the cases between 11 and 15 years of age.

Based on these autopsy studies, two alternative assumptions can be made:

1. Rheumatic fever is an extremely common disease. It may evolve in a severe form which is clinically diagnosed; it may also develop as a discrete process which is not followed by crippling valvular lesions and which may cause "innocent" murmurs either during the entire life or for some years. Physical signs typical of heart disease may regress and even disappear. According to Bland, Jones and White,[41] "It is probable that in the majority minimal scarring without significant valve deformity remains, notwithstanding the absence of characteristic murmurs." This statement is particularly significant because it was made following the study of 1,500 children and adolescents with rheumatic fever, in a great majority of whom the murmurs disappeared in the first 10 years after the acute stage of the disease.

2. In addition to rheumatic fever, other processes (allergic reaction to nonbacterial antigens; mild bacterial lesion of the valves?) may cause fusion of the valvular commissures which has no evolutionary tendency and fails to cause severe stenosis.

Our investigation on the QT interval failed to disclose any abnormal prolongation of electric systole in children with murmurs. The laboratory tests performed by Friedman, Robie and Harris [28] in some children with a "vibratory" murmur failed to disclose evidence of previous streptococcal infection or an active inflammatory process. However, this study cannot

exclude nonstreptococcal allergy or possibly a different, more discrete form of rheumatic fever.

If the above two possibilities are taken into consideration, the clinical problem is reduced to the following:

Is there any clinical or graphic method for differentiating the "innocent" murmurs from the others? Our studies failed to produce such a method. Moreover, separation of the "innocent" murmurs from the others is impossible until prolonged studies demonstrate whether some of the children with "innocent" murmurs develop a rheumatic mitral stenosis in later years, and whether some of them have a congenital lesion. As long as many patients with mitral stenosis are diagnosed only in their twenties or thirties, and many patients with an atrial septal defect are diagnosed only in their thirties or forties, this separation is obviously impossible.

Practical advice is the following: Every physician should make a careful notation of the existence and character of *any* murmur of children. Future correlation between these protocols and the subsequent clinical evolution may shed light on the mechanism of production of these murmurs.

Summary

The problem of systolic murmurs in children and adolescents is considered in general and a review of existing literature is made. The terms "functional," "innocent" and "physiologic" are discussed in reference to these murmurs.

A clinical and graphic study was made in 500 unselected children between the ages of four and 17. Clinical auscultation was made by three examiners. Electrocardiograms and phonocardiograms were recorded in all cases. Further clinical and graphic studies were made in 87 cases having louder murmurs. Fluoroscopy was done in 40 cases. Hematologic studies were made in 38 cases.

From a clinical point of view, a medium or loud systolic murmur was found in 23.3% of the cases, and no significant difference was found between the two sexes. Even though the majority of systolic murmurs were pulmonic, a fair number were heard at the apex and over the aortic area.

No correlation was found between murmurs and economic background or race.

No correlation was found between murmurs and height or weight.

Changes of the murmur with changes of position of the child or by rotating the neck were found to be inconstant and not relevant.

No prolongation of the QT interval was found in children with murmurs.

A phonocardiographic study revealed diastolic extra sounds in 63%, a split P_2 in over 50% of the cases.

A study of the configuration of the murmur and of the area where it was best recorded was further made. With faint murmurs excluded, 23% of the

children had murmurs in the tracing. The murmur was "musical" in over one-half of cases with murmurs. It was "diamond-shaped" in slightly less than one-half, and "in decrescendo" in more than one-half. This study would seem to indicate a mitral origin in over one-half, a pulmonic or aortic origin in the rest. In 6.5% of the cases, significant differences were found between clinical examination and phonocardiographic findings.

No difference was found as to anemia between children with murmurs and children without.

Fluoroscopy revealed a dilated and strongly pulsating pulmonary artery in 75% of children with louder murmurs.

The following possibilities were considered and excluded:

(a) That the murmur is inherent in the size and configuration of the cardiovascular system of children.
(b) That it is caused by a disproportion in the development of heart, vessels and ostia.
(c) That it is due to compression of the pulmonary artery by the chest wall.
(d) That it is an extracardiac murmur, or is due to anemia, or is originating in the neck.

It was also excluded that the systolic murmur of children has different clinical or graphic characteristics from those of "organic" murmurs.

The frequency of occurrence of these murmurs was not considered as implying a "physiologic" origin; many diseases of man are more common without being physiologic.

Autopsy studies on large series of persons of various ages have revealed the extreme frequency with which the cardiac valves present minor damage. This frequency increases with age; lesions were found in 20% between the ages of 11 and 15. The coincidence of this figure with that of medium or loud murmurs observed by the authors is striking. These minor valvular lesions were considered by pathologists as being of rheumatic nature. However, further proof of this may be needed.

The authors present two alternative hypotheses:

(a) That the murmurs are caused by a discrete rheumatic process which has different characteristics from the more severe forms and which, in the majority of cases, is not followed by important valvular lesions.
(b) That the murmurs are due to nonrheumatic, possibly allergic valvulitis, with no tendency to increase in severity.

In either case, they consider it impossible to separate these murmurs from those of valvular lesions which have greater clinical significance. Therefore, they advise careful notation of all murmurs and repeated studies through the years. Mitral stenosis would never be accidentally discovered between 20

and 40 if careful, systematic studies of children were made and observations were continued until a murmur either disappears or becomes definitely significant.

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SUMMARIO IN INTERLINGUA

Le problema de murmures systolic in juveniles e adolescentes es discutite in general. Un revista del existente litteratura es presentate. Le terminos "functional," "innocente," e "physiologic" in lor application a iste murmures es analysate.

Esseva effectuate un studio clinic e graphic in 500 non-seligite individuos de etates de inter 4 e 17 annos. Electrocardiogrammas e phonocardiogrammas esseva obtenite in omne casos. Studios clinic e graphic additional esseva effectuate in 87 individuos qui habeva murmures plus forte. Fluoroscopia esseva usate in 40 casos. Studios hematologic esseva facite in 38 casos.

Clinicamente, un moderate o forte murmure systolic esseva trovate in 23,3% del casos. Le incidentia non differeva significativemente pro le duo sexos. Ben que le majoritate del murmures esseva pulmonic, un numero non negligibile esseva audite al apice e super le area aortic.

Nulle correlation esseva constatate inter murmures e milieu economic, altor, o peso.

Un studio phonocardiographic revelava sonos accessori diastolic in 63% del casos, un P_2 fisse in plus que 50%.

In plus, un studio esseva facite relative al conformation del murmures e al area de lor registration optimal. Sin contar murmures de grado debilissime, 23% del juveniles habeva murmures in lor registrationes. Le murmure esseva "musical" in plus que un medietate del casos in que murmures esseva presente; illo esseva "rhombic" in levemente minus que un medietate; illo esseva "in decrescendo" in plus que un medietate.

Fluoroscopia revelava un dilatate arteria pulmonar con forte pulsation in 75% del individuos con forte murmures.

Le sequente possibilitates esseva prendite in consideration e rejicite: (a) Que le murmure es inherente in le dimension e configuration del systema cardiovascular de juveniles; (b) que illo es causate per un disproportion in le disveloppamento de corde, vasos, e ostios; (c) que illo resulta de un compression del arteria pulmonar per le pariete thoracic; e (d) que illo es extracardiac o resulta de anemia o ha su origine in le collo.

Esseva etiam rejicite le possibilitate que le murmure systolic de juveniles differe in su characteristicas clinic o graphic ab le murmures "organic."

Le frequentia de iste murmures non esseva interpretate como un indication que illos es de origine "physiologic." Il existe multe morbos que es plus commun sed que non es physiologic.

Studios necroptic in extense series de individuos de varie etates ha revelate le alte frequentia con que le valvulas cardiac exhibi minor grados de defectuositate. Iste frequentia cresce con le etate del individuos. Lesiones esseva trovate in 20% del casos in le gruppo de etate de inter 11 e 15 annos. Le coincidentia de iste cifra con illo de moderate e forte murmures observate per le autores es significative.

Le autores presenta duo hypotheses alternative: (a) Que le murmures es causate per un discrete processo rheumatic que differe in su characteristicas ab le formas plus

sever e que, in le majoritate del casos, non es sequite per importante lesiones valvular, o (b) que le murmures es causate per un valvulitis non-rheumatic, possibilemente de character allergic, que exhibi nulle tendentia a augmentar su grado de severitate. In ambe casos, le autores considera como impossibile separar iste murmures ab le murmures de lesiones valvular con plus grave signification clinic.

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VALUE OF AMINOPYRINE*†

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Modern medical science has made such tremendous strides in the field of therapeutics that many older drugs, especially if potentially productive of untoward and dangerous side-effects, have been discredited and have fallen into disuse. Admittedly, many such drugs have marked therapeutic value and are deserving of further investigation and clinical trial before they are completely discarded.

Aminopyrine, by force of historical circumstances, has been such a discredited drug for many years.[1, 2a, 3c, 4b, 5, 6, 7, 8] The danger of agranulocytosis resulting from its use is real and well established, but undoubtedly has been overemphasized.[1, 2a, 4b, 5, 6, 7, 8] Its value as a potent antipyretic is well known and needs no extensive elaboration. It is the purpose of this paper to show that it may be effective where other antipyretics have failed, but particularly that, by means of its potent antipyretic properties, acting in a purely nonspecific manner, it may be a life-saving drug under conditions in which even the most powerful and specific of the newer drugs have failed. Six cases are presented to prove these contentions.

Let us say at once that it is not our purpose to encourage the resumption of the widespread, reckless, indiscriminate and uncontrolled use which this preparation once enjoyed; but to show that under carefully controlled clinical conditions it is still a uniquely valuable drug which deserves to be remembered and used in particular circumstances by all physicians.[9, 2a]

Pharmacology

Aminopyrine has long been known as an effective antipyretic and analgesic. It is a pyrazolone compound which in many ways resembles the salicylates in general pharmacologic properties.[2b] Administered orally, it is rapidly excreted, and after moderate doses it appears in the urine after two hours.[10] Long-continued administration has no cumulative effect, nor is there an increase in tolerance.[10, 11] Antipyretic effects of the drug are achieved by direct action on the hypothalamus through its effect on the thermoregulating centers in the brain, rather than by any primary effect on

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† The terms "aminopyrine" and "amidopyrine" are used interchangeably in the literature, often in the same article, and refer to the same substance. The term "aminopyrine" is used here as probably being the more nearly correct.

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heat production or heat dissipation.[2c, 3a, 10, 12] A fall in oxygen consumption follows rather than precedes defervescence, and the temperature drops even though sweating is blocked by atropine. The reported antidiuretic effect of the drug in cases of diabetes insipidus supports the concept of an action on the hypothalamus.[4c, 13, 14, 15, 16] Aminopyrine relieves pain, particularly pain arising in integumental structures as observed in headache, neuralgia and myalgia, without affecting consciousness.[2c, 3b, 12] The suggestion has been made that its effectiveness in relieving headache is due in part to mobilization of excess water;[3c] and in relieving joint pain, to reduction of joint effusions.[2d] For some patients, aminopyrine may be more potent as an analgesic than are the opiates. It has been reported that relief of pain in some cases of migraine, tic douloureux and tabetic crisis can be induced with aminopyrine when none of the other analgesics, including opiates, are adequate.[10]

Aminopyrine, except in large doses, has no effect on normal temperature. In pyrexia, however, it appears to reset the thermostat for normal temperature and lowers the temperature by increasing the dissipation of heat.[2c, 3b, 10] Most authorities attribute this to increased peripheral blood flow and sweating. The fact that salicylates can lower temperature even when diaphoresis is prevented by atropine [3a] would seem to indicate that vasodilatation is the more important of these two actions.

The remarkable similarity in the nonspecific effects of aminopyrine to those of the corticotropic and adrenocorticoid steroids and the evidence of hypothalamic effect of aminopyrine have led to speculation that it may exert its antipyretic and antiphlogistic effect by stimulating the production and secretion of adrenal corticosteroids into the blood stream. Work along this line has led to the demonstration of a fall in absolute eosinophil count and increase in excretion of 17-ketosteroids in the urine during the administration of aminopyrine.[17, 18] Further investigation along similar lines, particularly as to increased excretion of other corticoids in the urine, is obviously desirable before this point of view can be accepted.

Historical Background

Aminopyrine was discredited because of its toxic effects on the bone marrow, with the production of leukopenia, neutropenia and agranulocytosis which sometimes proved fatal. Aminopyrine was the first of a series of drugs to be associated with this toxic complication.[1, 2a, 3c] Most of these cases of severe reaction were reported during the decade between 1930 and 1940, when the drug was sold indiscriminately over the drug store counter. It was during this period too, that the drug was often included in proprietary preparations for self-medication.

Kracke and Parker in 1935 presented a complete review of the relationship of aminopyrine administration and granulocytopenia, beginning with the description of the first reported case by Shultz in Germany in 1922 and by

Lovett in the United States in 1924.[1] The resumé cites every known case reported in the literature and all of the experimental studies to the date of publication. Chief among these latter was the work of Weiskotten, who demonstrated the marked neutropenic effect of benzene on the hematopoietic system of rabbits, and Selling, who made a study of three cases of profound leukopenia and hemorrhage due to industrial benzene poisoning. Kracke's description in 1931 of an acute fulminating granulocytopenia following the ingestion of large quantities of acetphenetidin was the first clinical intimation of this type of drug intoxication. This was followed by Kracke's report in 1932 of nine cases, eight of whom had taken coal tar derivatives. A virtual flood of reports followed from all over the world, so that Kracke in his review was able to record a total of 172 cases following drug administration; 153 followed the use of aminopyrine alone or in combination with other drugs.[1] The remaining cases involved dinitrophenol, acetanilid and Neostibosan. The relationship between aminopyrine and agranulocytosis was thus firmly established.[1, 2a, 3c, 4b]

It was estimated that in 1934 a total of 30 million prescriptions for aminopyrine were written in the United States alone,[2a] in addition to the large quantity of the drug purchased over the counter or as a component of various nostrums advertised for headache, arthritis, dysmenorrhea, and similar self-treated disorders. During the same period only 145 new cases of agranulocytosis were reported from all sources.[1] The possibility of producing agranulocytosis in any individual patient is therefore remote.[3, 9, 19, 21, 22] Even when the drug was widely used, granulocytopenia was not a common sequel.[1, 2a, 5] This is in accord with Resenikoff and others, who point out that when one considers the enormous amount of aminopyrine consumed and the relatively few affected with granulocytopenia, it is obvious that one is dealing with the question of sensitivity in certain patients, rather than with the universal action of the drug.[9, 22, 23, 24] The Council on Pharmacy and Chemistry of the American Medical Association [9] seemed to agree with this statement when it went on record discouraging the indiscriminate administration of aminopyrine, but stated that since it was a valuable drug it had its place in therapeutics under well controlled conditions under the supervision of a physician. Kracke, while being chiefly responsible by his review and disclosures for the abandonment of the use of aminopyrine was nevertheless of the same opinion.[1]

Case Reports

Case 1. A 38 year old physician was hospitalized on October 2, 1940, because of a spiking fever of unknown origin. Chronic sore throat had first appeared in the middle of July of that year, and early in September the patient had developed joint pains after a game of golf. Since September 15, after an evening of bowling, he had been confined to bed with intermittent joint pains, spiking fever with chills, and profuse sweating. The sweating was so severe as to be one of the main disabling symptoms. Salicylates and aspirin aggravated the sweating, did not affect the fever,

and were not well tolerated. Sulfonamides caused nausea and vomiting, and were discontinued. The fever, drenching sweats, malaise and arthralgia completely exhausted and incapacitated the patient. He was miserable and despondent, refused to be shaved or to eat, and by the time of hospitalization had lost 30 pounds.

On admission the patient appeared acutely ill and was covered with perspiration. The face was flushed, the tongue dry and coated. The temperature was 101° F.; pulse, 96 and regular; respirations, 22; blood pressure, 120/80 mm. of Hg. The teeth were in poor condition. The tonsils were absent; the pharynx was hyperemic and injected. There were some yellow exudative patches in the left tonsillar fossa. A submaxillary lymph gland on the left side the size of a cherry was nontender, and had been present since the patient was 12 years old. The heart was not enlarged; a faint, short, early diastolic murmur was audible at the pulmonic area. The lungs were clear. The tip of the spleen was palpable on inspiration, and was soft in consistency. Petechiae were absent. The urine contained a trace of albumin, but microscopic hematuria and other abnormalities were absent. Blood hemoglobin was 87%, red blood cells, 4,760,000; white blood cells, 13,200, with a normal differential. The blood sedimentation rate was 97 mm./hr. by the Westergren method.

A tentative diagnosis was made of streptococcal pharyngitis and infectious arthritis, with rheumatic fever and subacute bacterial endocarditis to be excluded. Sulfathiazole was prescribed, and 100 c.c. of antistreptococcus convalescent serum were administered intravenously.

In the following 10 days the septic fever continued unabated, rising to 103.4° F. rectally daily, and associated with frequent chills and continual profuse sweating. On October 5, three days after the patient's admission to the hospital, aspirin, gr. 10 three times a day, was substituted for the sulfathiazole. On October 8 aspirin was discontinued because of the intolerable increase in sweating which it caused without in any way affecting the fever or clinical picture.

A complete diagnostic study, including examination of blood smears for malaria, repeated blood cultures, animal inoculations, and agglutination tests for typhoid, paratyphoid and brucellosis, skin test for brucellosis, nose, throat, urine and stool cultures, and x-rays of the chest, nasal accessory sinuses and teeth, was negative. Mantoux test with 1–10,000 O.T. was positive. Therapeutic test for malaria with quinine sulfate, gr. 10 three times a day for two days, was negative. The patient complained on occasion of joint pains in the fingers and toes. A small, flame-shaped hemorrhage was noted beneath the nail of the right big toe.

Aminopyrine, gr. 10 four times a day, was started on October 12 as a last resort. The next day the patient was afebrile all day for the first time since the onset of fever on September 15. On October 15, since he was still afebrile, the dose of aminopyrine was reduced to gr. 5 three times a day; that evening the temperature rose to 101° F. The next day the dose was raised to gr. 10 three times a day. The temperature again subsided to normal and remained so until October 28. During this period the daily white blood cell count varied between 11,900 and 16,500. On October 28, because of the report of a sudden drop in the white blood cell count to 7,500, aminopyrine was discontinued. The temperature immediately began to rise, and in the evening of October 30 reached 103° F. On October 31, the white blood cell count being 14,700, aminopyrine, gr. 10 three times a day, was started again. On November 1, the highest temperature recorded was 99.4° F., and thereafter the patient became and remained afebrile throughout his hospital stay. The profuse and debilitating sweating diminished rapidly and disappeared within two weeks, and simultaneously the patient's general condition, appetite and morale steadily improved. On December 16 the white blood cell count was 14,500; sedimentation rate, 29 mm./hr. On December 23 the patient sat in a chair for 20 minutes; by January 14 a weight gain of 10 pounds was recorded, and the patient was up and about for several hours daily.

Occasional rawness in the throat, slight pain and stiffness in the finger joints on arising in the morning, and barely palpable splenomegaly persisted. On January 23 the patient was discharged, still taking aminopyrine, to convalesce at home.

The patient continued to take aminopyrine in gradually decreasing doses for the next four months, with periodic checks on the white blood count and differential, which remained within normal limits. By this time recovery was apparently complete, and he has had no recurrences to the time of this writing, in spite of an active and sometimes rigorous life. He served on active combat duty throughout the Aleutian campaign in World War II, and since discharge from the Army has been practicing medicine.

Comment: The favorable and in this case probably life-saving effect of aminopyrine is apparent. Although the exact cause of the fever was never ascertained, there is no reason to suppose that aminopyrine had any specific influence in eradicating it, as the long course of the disease following symptomatic relief with this drug indicates. This was also demonstrated by the return of symptoms and fever when the drug was temporarily discontinued

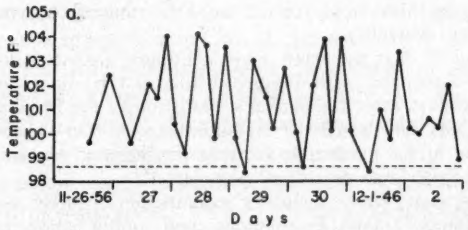

FIG 1A. *Case 2.* Periarteritis nodosa. Temperature curve 11/26/46 to 12/2/46, representative of entire five-week period in hospital from 11/26/46 to 1/2/47, date on which aminopyrine therapy was started.

or reduced in dosage. It is of interest that the degree of reduction in fever was proportional to the dosage of the drug within the therapeutic range. It is important to note that a drop in the white blood count did appear once at the height of the dosage of the drug, but did not become serious, and was readily controlled by a reduction in dosage.

Aspirin did not affect the fever, produced increased perspiration and was not tolerated. The sulfonamides caused toxic side-effects. Aminopyrine produced a prompt and sustained drop in temperature, with improvement in the patient's symptoms, morale and appetite. The continuous administration of the drug, guarded by frequent blood counts, eliminated the wasting fever and sweating, which were the main causes of discomfort, exhaustion and discouragement. Symptomatic relief gave the patient time to build up his own body defenses until a spontaneous cure was effected.

Case 2. A 51 year old white male was observed at intervals from November, 1946, through June, 1948. During this period he was hospitalized four times for exacerbations of his illness, which was diagnosed from a muscle biopsy during the second admission as periarteritis nodosa.

First Admission: During the first admission (November 26, 1946, to February 19, 1947), the clinical course was characterized chiefly by spiking fever with chills and profuse sweating which had persisted for a month.

The patient became progressively weaker despite the administration of sulfadiazine, penicillin, salicylate and Pyribenzamine therapy. On December 10 some favorable response was noted to streptomycin, but this was not sustained. Atabrine was substituted for streptomycin, without effect. Aminopyrine was started on

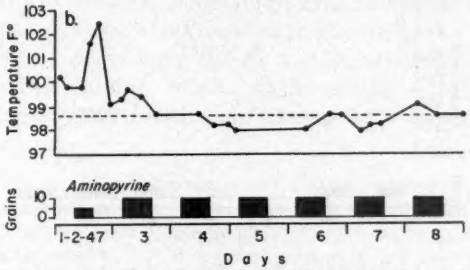

FIG. 1B. *Case 2.* Periarteritis nodosa. Effect of aminopyrine; temperature curve from first day of administration of aminopyrine.

January 3 and brought about prompt remission of fever and sweating (figures 1 A, B, C, D). With the sustained control of fever the patient's general condition improved. He was able to eat and sleep, and the progressive loss of weight was halted. The underlying disease process, however, continued its typically erratic course. During the following seven weeks there were several episodes of pain and muscle tenderness, necessitating the use of opiates in addition to aminopyrine. Repeated hemograms showed the presence of anemia and a high sedimentation rate.

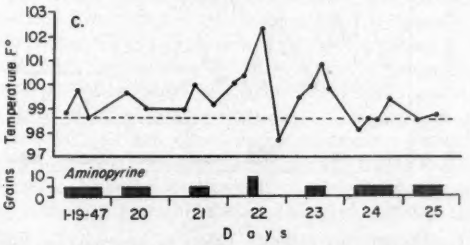

FIG. 1C. *Case 2.* Periarteritis nodosa. Effect of trial reduction in dose of aminopyrine.

With the control of fever and sweating, supportive therapy brought general improvement as well as subsidence of pain. The patient was discharged on February 19, with instructions to continue taking aminopyrine, 5 gr. three times daily, and to report twice weekly for a white blood cell count.

The patient did well on this régime for two months, remaining afebrile and gaining weight; at this point aminopyrine was discontinued. On May 2 he noted blood in his urine, followed by fever and generalized aches and pain.

Second Admission: The patient was re-admitted for these reasons on May 6. There were a few petechiae on the soft palate and on the roof of the mouth.

Biopsy of a painful nodule which had appeared in a leg muscle established the diagnosis of periarteritis nodosa.

Again, aminopyrine controlled the fever (figure 1E) but not the pain, which required opiates. These pains gradually subsided, and the patient was discharged on June 12, feeling well, and with instructions to continue taking aminopyrine and to return regularly for routine blood counts.

Third Admission: The patient was admitted for the third time on July 28, 1947, because of an outcropping of exquisitely tender subcutaneous nodules over most of the body.

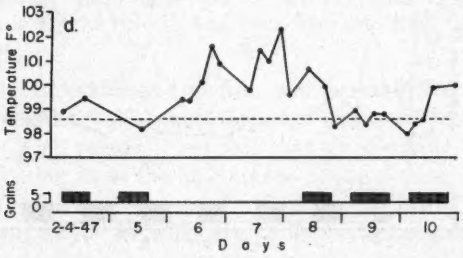

FIG. 1D. *Case 2.* Periarteritis nodosa. Effect of trial cessation of aminopyrine.

Red blood cells numbered 4,330,000, with 81% hemoglobin. White cells numbered 12,430 on admission, and in the next three days 10,900, 8,700 and 5,900, successively.

Fever was again promptly controlled by aminopyrine. The lesions disappeared and the patient was discharged on July 31 with instructions to continue taking aminopyrine and to report for frequent examinations. He was soon well enough to work full time, and during the next 11 months gained 16 pounds.

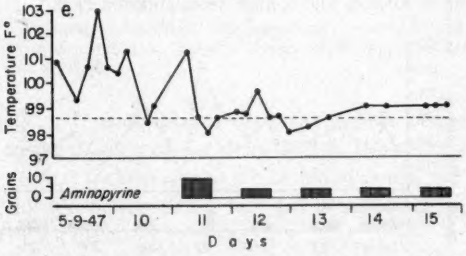

FIG. 1E. *Case 2.* Periarteritis nodosa. Effect of aminopyrine (second admission).

Fourth Admission: A fourth admission was necessary on June 4, 1948, because of the sudden onset of severe abdominal pain, associated with hematuria, headache, fever, leukocytosis and pain in the flank suggestive of kidney infarction. Moderate hepatic enlargement was noted.

With a temporary increase in dosage of aminopyrine the fever was again brought under control, and the pain and urinary tract symptoms regressed. The patient was discharged on June 25 in good condition. On follow-up eight years later he was active and working, was no longer taking aminopyrine, and had no fever, but still experienced occasional neuritic pains.

Comment: In this case of periarteritis nodosa proved by biopsy, aminopyrine was administered as symptomatic therapy to control the picket-fence

type of septic fever, chills, profuse sweating, anorexia and weight loss. This medication had no apparent effect on the disease process itself, which, notwithstanding almost continuous administration of aminopyrine, progressed in a typical fashion during the 19 months of observation. Remissions and exacerbations of the bizarre symptoms characteristic of this disease continued to appear. Frequent laboratory tests, repeated during each admission, consistently revealed leukocytosis, moderate to mild anemia, a high sedimentation rate, and characteristic abnormalities in the urine.

However, control of the fever and its associated symptoms removed the incapacitating and debilitating effects of the illness, restored the patient's appetite and strength, and permitted ambulation until spontaneous remission of the disease occurred.

Case 3. A 43 year old white woman was transferred to the medical ward on April 16, 1954, from a surgical ward to which she had been admitted on April 6, 1954, for a contemplated hysterectomy. She had had dysmenorrhea and menorrhagia for eight years prior to admission, and five years previously had been told that she had uterine fibroids which should be removed. She did not elect to follow this advice until chills, fever, abdominal pain and diarrhea occurred about a week before admission. During her stay on the surgical ward she had had a daily temperature of 101° F. to 103° F. which did not respond to 600,000-units of penicillin intramuscularly daily. Because of the fever, surgery was not performed, and the patient was transferred to the medical word for evaluation, since the gynecologist did not feel that the fever was due to degeneration or infection of the uterine fibroids.

Physical examination at the time of transfer revealed a temperature of 101° F.; pulse, 104, grossly irregular; blood pressure, 110/60 mm. of Hg. Mitral stenosis and regurgitation were present. The uterus was enlarged to the umbilicus and was firm, irregular and slightly tender. There was no palpable splenomegaly, nor were petechiae found. Repeated urine examinations were negative except on one occasion, when three to five erythrocytes per high power field were found. The blood showed 3.60 million red cells, 65% hemoglobin, 8,600 white cells, and a normal differential count. Stools were reported negative on direct examination and culture, and urine cultures were negative. A chest roentgenogram was reported as showing enlargement of the left ventricular and pulmonary conus segments. Repeated blood cultures from April 16 to May 6, during which period penicillin was withheld, were negative. A sternal marrow culture taken four days after penicillin was started again was reported as showing a fungus, probably *Nocardia asteroides,* but this was not found on repeated cultures.

From April 16 to April 30 all treatment was withheld, and during this time the patient had daily temperatures of 101° F. to 103° F., chills, sweats and malaise. On April 30 sodium salicylate, gr. 10 four times daily, was started, with no change in symptoms or temperature course. On May 6, because of the continued unexplained fever, cardiac murmurs, and a single subungual splinter hemorrhage, treatment of the patient for subacute bacterial endocarditis was instituted despite the absence of splenomegaly, embolic phenomena or positive blood cultures. She was given 2,000,000 units of aqueous penicillin intramuscularly every two hours, and 600,000 units of procaine penicillin intramuscularly four times daily the first day, then procaine penicillin, 600,000 units four times daily, and streptomycin, 0.5 gm. twice daily. There was no discernible change in either symptoms or temperature course.

On May 12 the penicillin dosage was changed to 5,000,000 units by intravenous drip twice daily. On this dosage the temperature slowly subsided to normal in 10

days, but then rose to 103° F. on the following day. Penicillin was increased to 2,000,000 units every three hours, without effect. By June 2 fever was high again, the temperature reaching 103° F. daily; the patient had lost 20 pounds, was depressed, and threatened to leave the hospital because of the pain and the many tender nodules that had developed at the site of the antibiotic injections. Medication was halted on this date.

Seven days later, on June 9, aminopyrine therapy was begun with a dosage of 10 gr. four times daily. The temperature dropped to normal in the first 24 hours, and for the first time since admission the patient stated that she felt better. The drug was continued but was gradually reduced to 5 gr. three times daily, while frequent white blood counts were obtained. At no time after the institution of aminopyrine therapy did the patient have a fever; the sweating ceased, appetite improved, and strength returned. By June 25 the patient was able to return to her home on restricted activity, still taking 5 gr. of aminopyrine three times daily, which she continued for four months. She returned for regular blood counts. She was seen one year later, entirely well (except for the chronic cardiac murmurs and uterine fibroids), afebrile, and with a normal blood count.

Comment: In this case, as in case 1, it is likely that aminopyrine, although acting in a nonspecific manner, was nevertheless a life-saving drug. It now seems likely that the prolonged febrile episode was due to an acute exacerbation of rheumatic carditis, rather than to subacute bacterial endocarditis. Symptomatic therapy and control of the fever with its disabling and debilitating concomitant symptoms by aminopyrine, after many millions of units of penicillin and many grams of streptomycin failed to accomplish this, supported the patient in a comfortable state until spontaneous resolution of the disease process took place.

Case 4. A 39 year old white woman was admitted to the hospital on September 11, 1954, with a diagnosis of ulcerative colitis, and rheumatic heart disease with mitral stenosis. There was a history of rheumatic fever at the age of 12, and of recurring diarrhea provoked by ingestion of raw fruit or vegetables for years. The patient had delivered an erythroblastotic infant in November, 1953, and since then had had four subsequent admissions, totaling 118 hospital days, because of diarrhea, abdominal pain, anemia, dehydration and prostration. During these admissions the diagnoses mentioned were established by clinical, roentgenographic and sigmoidoscopic examinations. The possibility of subacute bacterial endocarditis or specific bowel infection was excluded by repeated blood and stool cultures, by agglutination tests, and by repeated fruitless search of stool specimens for *Endamoeba histolytica.* The symptoms subsided each time following conservative therapy consisting of high caloric diet, transfusions, vitamins and antibiotics. On the last previous admission, in June, 1954, parenteral corticotropin had been instituted, and had been continued in dosage of 40 units daily at home.

On September 8 the patient had chills, fever, vomiting, colic and diarrhea. She was admitted on September 11 with a fever of 105° F., acutely ill and dehydrated. Blood cultures (including two for anaerobes), stool cultures and a urine culture were made prior to administration of antibiotics. On September 13, Streptomagma orally and procaine penicillin parenterally were begun; 40 units of ACTH intramuscularly daily were continued. On September 21, streptomycin parenterally and Gantrisin orally were added, and the dosage of penicillin was increased. Despite this therapy the temperature spiked daily to between 101° F. and 104° F. By this time, all cultures had been reported negative except for *E. coli* and *Aerobacter aerogenes* in the

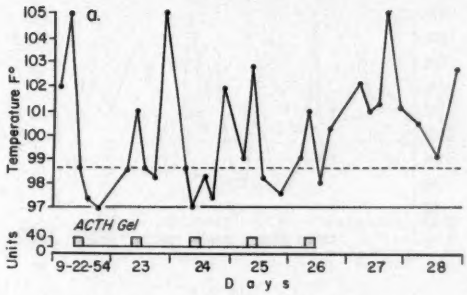

FIG. 2A. *Case 4.* Ulcerative colitis. Temperature curve for week of 9/22/54 to 9/28/54, representative of entire period in the hospital from 9/11/54 to 10/2/54. No effect of ACTH gel on fever.

stool. Administration of Diodoquin and chloroquine as well as Chloromycetin was begun on September 23. On September 26 chills, fever and sweats were still present; corticotropin was discontinued.

Aminopyrine was started in a dosage of 5 gr. four times daily on October 2. Fever mounted to 105° F. on October 3, but subsided precipitously to normal thereafter (figures 2A, B), as did the chills and profuse sweating. On October 12 all medication except the aminopyrine was discontinued; the patient was eating well and regaining weight and strength.

On October 20, fever rose again to 102° F., and abdominal pain developed. By October 25 it was evident that a perforation of the colon had occurred; antibiotics were reinstituted and an ileostomy was performed. The patient made a stormy recovery and is presently awaiting a colectomy.

Comment: Aminopyrine did not cure this patient, but did afford a dramatic respite from fever which was refractory to all other treatment, including antibiotics and ACTH for 17 days. During this respite she recovered much weight and strength, and was thereby no doubt in much better condition to withstand the operation for the perforation of the colon which developed later.

Case 5. A 33 year old woman was hospitalized on November 29, 1948, with an illness of six weeks, during which period of time she had been confined to bed by a

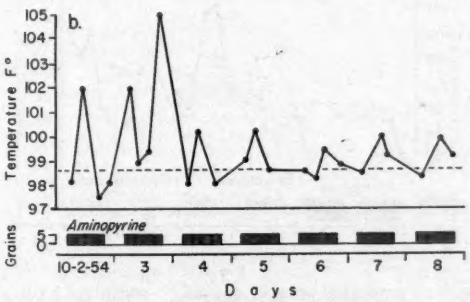

FIG. 2B. *Case 4.* Ulcerative colitis. Effect of aminopyrine from first day of administration.

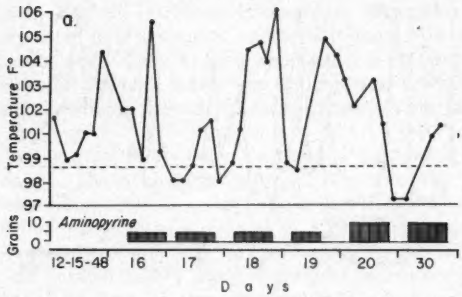

FIG. 3A. *Case 5.* Carcinoma of the pancreas. Temperature curve for week of 12/15/48 to 12/21/48, representative of course from day of admission to hospital on 11/15/48.

daily spiking fever, shaking chills, profuse sweats, anorexia, marked weight loss and profound weakness. Following hospitalization these symptoms continued in spite of treatment with sulfonamides and antibiotics. Progressive jaundice and a mass in the right upper abdominal quadrant appeared. Because of the high fever, wasting and

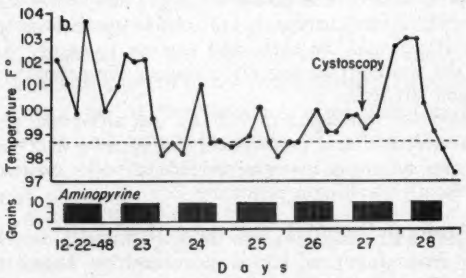

FIG. 3B. *Case 5.* Carcinoma of the pancreas. Gradual effect of aminopyrine, 40 gr. daily, with subsidence of fever by lysis except for fever spike following cystoscopy.

debility, the patient was considered to be too poor a risk for exploratory laparotomy. Aminopyrine was started on December 16. The effect of the drug on the fever is illustrated in figures 3A, B and C. A dosage of 5 gr. four times a day was associated with no change in the fever, but on 10 gr. four times a day there was a gradual sub-

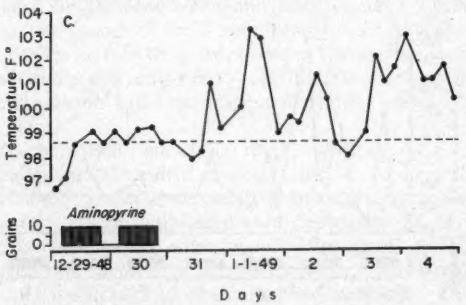

FIG. 3C. *Case 5.* Carcinoma of the pancreas. Final subsidence of temperature to normal on aminopyrine, 40 gr. daily. Immediate recurrence of spiking fever with cessation of aminopyrine administration.

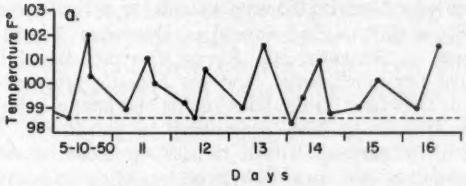

FIG. 4A. *Case 6.* Carcinoma of the pancreas. Temperature curve from 5/10/50 to 5/16/50, representative of fever curve from date of admission on 4/26/50.

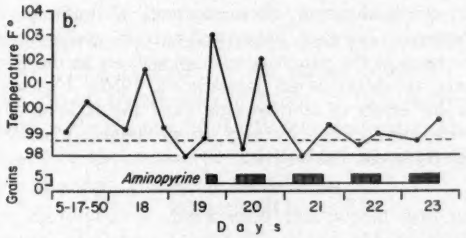

FIG. 4B. *Case 6.* Carcinoma of the pancreas. Effect of aminopyrine.

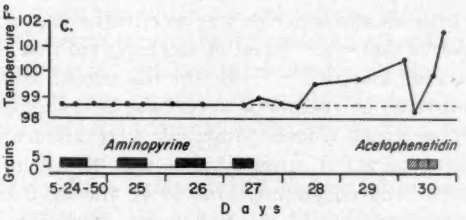

FIG. 4C. *Case 6.* Carcinoma of the pancreas. Continued effect of aminopyrine. Return of fever with cessation of aminopyrine. Acetphenetidin started.

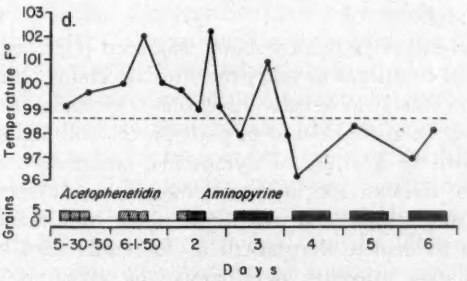

FIG. 4D. *Case 6.* Carcinoma of the pancreas. Persistent spiking fever while acetphenetidin was being administered; return of temperature to normal with cessation of acetphenetidin and resumption of aminopyrine.

sidence of fever by lysis (interrupted only by a fever spike following cystoscopy on December 27, 1948), until it reached normal on December 28, and remained so until the drug was stopped on December 30. During this time the chills and sweats also subsided, the patient felt much better, and her appetite returned. When the drug was discontinued on December 30 the fever, chills and sweats returned as severely as before, and were not relieved until laparotomy on January 3, 1949. Exploration revealed the cause of the patient's trouble to be a carcinoma of the head of the pancreas, with a dilated gall-bladder and biliary tree, ascending cholangitis, and cholangitic liver abscesses. Cholecystojejunostomy provided drainage of the biliary tract, and following this the fever subsided and remained normal without further medication. The leukocytosis provoked by the infection was not affected by the aminopyrine.

Case 6. A 46 year old man was admitted to the hospital on May 18, 1950, with symptoms of fever, chills, sweating, anorexia, nausea, vomiting, wasting, abdominal pain, deep and progressive jaundice, pallor and anemia, and a large nodular liver due to carcinoma of the head of the pancreas with metastases to the liver, which had been discovered elsewhere at operation on January 14, 1950. Figures 4A, B, C and D illustrate the favorable effect of aminopyrine (and the lack of effect of phenacetin) on the fever, which had been refractory to prolonged treatment with penicillin, chloramphenicol, Terramycin and aspirin.

Discussion

Aminopyrine has been administered in a variety of febrile diseases, including measles, rheumatic fever, pneumonia, influenza, scarlet fever, meningitis and malaria, and, except in the last, was found effective in controlling fever.[6, 10, 25] In measles aminopyrine was so effective that some investigators regarded it as specific therapy,[10, 25] but others reported that the natural course of this disease was not affected.[10, 26] Before the advent of the corticosteroids the use of aminopyrine in rheumatic fever was investigated, with the consensus that in those cases whose symptoms were refractory to salicylates, or when salicylism occurred, aminopyrine was the drug of choice.[3a, 4a, 6] Some investigators believed aminopyrine to be the drug of choice in most cases of rheumatic fever, since it acted more promptly, was effective in smaller doses, and produced fewer toxic effects than did the salicylates.[10, 27, 28, 29] Like the salicylates, aminopyrine reduced the pain, immobility, swelling and inflammation of the joints, but did not benefit the cardiac lesions or the subcutaneous nodules.[2b, 29]

Fever, unless excessive or prolonged, has been regarded historically as a favorable reaction to infections and other disease states. Its absence, as the absence of leukocytosis, in severe infections, especially in the aged or debilitated, has long been considered of poor prognostic import. Fever, however, carries with it a train of symptoms including malaise, headache, arthralgia, chills, diaphoresis, anorexia, nausea, restlessness, sleep disturbances, delirium and stupor. If prolonged, these may result in debility and exhaustion, and so deplete the patient as to render him susceptible to aggravation of existing infection, development of secondary infection, thrombosis and embolism, intoxication by electrolyte and acid-base imbalance, starvation, and failure of function of vital organs; and so lead indirectly

to death even in otherwise intrinsically nonfatal or not necessarily fatal disease. The associated symptoms may constitute the entire clinical manifestations of the disease. Ideally, the cause of the fever should be removed, but occasionally, as in the cases here reported, the cause of the fever is either unknown or not susceptible to definitive therapy, so that the effects of the pyrexia itself constitute a threat to life. Spectacular improvement may ensue with reduction or elimination of the fever and its consequent attendant symptoms.

That potent and effective nonspecific treatment which leads to rapid control of fever can give the effect and illusion of the action of a specific drug has been recognized even in the past in the remarkably potent action of the salicylates in rheumatic fever. So prompt and marked is this effect as to have led to speculation that a specific action, as yet unknown and unexplained, is involved. The rapid resolution of joint pain, swelling, redness, immobility, tenderness and effusion, and the reported rapid absorption of pericardial fluid in cases of rheumatic pericardial effusion on administration of salicylates, lend some support to such speculation.

Experience in the last few years with the potent and nonspecific therapeutic effects of corticotropin and the corticosteroids has demonstrated and supports the concept that fever and its associated symptoms, as well as other nonspecific symptoms common to a wide variety of apparently unrelated diseases, may constitute the entire clinical picture of disease. So that, in some cases, when these are controlled the patient may appear well even when dying of an underlying serious and fatal disease. Other patients by such symptomatic treatment may be cured of an illness which seemed to be progressing to a rapid and fatal termination in spite of the application of potent specific medication.

These experiences have demonstrated that in many cases it is not the etiologic irritant in disease, but nonspecific symptoms of the type being discussed, representing tissue reactions to the etiologic irritant and basic illness, which constitute the entire manifest disease. Any agent which can suppress the deleterious tissue reaction during the active phase of the disease may suppress the active disease manifestations, thereby leading to improvement of appetite, gain in weight, strength and morale, and loss of toxicity which result in cure of the disease in an entirely nonspecific way, but in the manner of a specific drug. The very potent corticosteroids have transferred emphasis to and illuminated the beneficial and life-saving effects of nonspecific therapy (which in less potent form was once the only available type of treatment in most diseases) from specific treatment which resulted from the introduction of powerful chemotherapeutic and antibiotic agents in the immediately preceding but still recent historical period. This is not to say that specific therapy and nonspecific therapy are mutually antagonistic; rather, they may complement each other. Overwhelming and fulminant infections in some instances may be curable only by a combination of potent nonspecific

treatment such as corticosteroids, and specific treatment with chemotherapeutic and antibiotic agents, where each alone would fail.

Whether the favorable effect of aminopyrine on a wide variety of unrelated diseases is entirely due to its nonspecific action as a potent antipyretic, or whether a more fundamental action is involved, and whether it acts in a manner similar to or by stimulating the secretion of corticotropin and corticosteroids are unknown, and remain as problems for the future. In case 4 aminopyrine controlled fever when ACTH in presumably adequate dosage failed to do so.

As is well known, agranulocytosis as a reaction to or side-effect of drug action is not peculiar to aminopyrine alone, but occurs frequently in conjunction with other commonly used medicaments such as the sulfonamides, chloramphenicol, streptomycin,[4b, 32, 40, 42] thiouracil derivatives,[33, 36, 38, 39] Mesantoin and Tridione,[30] the antihistamines,[22, 31] and other important medicaments.[9, 34, 35, 37, 41] This possible complication to the use of such drugs has banned only their careless or unsupervised use, not their cautious and controlled administration with full knowledge of their possible harm balanced against their favorable action in certain disease states.

The danger of agranulocytosis from the use of aminopyrine is no less real today than it was in the past, but its actual incidence is very small, and the treatment of this condition (with antibiotics, corticosteroids and ample available supplies of blood for transfusion), should it occur, is more successful than formerly. Moreover, it need not occur at all if the drug is given under strict supervision, with frequent blood studies during the period of its administration.

The most commonly used alteratives today for the symptomatic treatment of fever and its associated symptoms and for other nonspecific symptoms are corticotropin and the corticosteroids. These have been accepted enthusiastically and to a great degree uncritically by the medical profession, and are widely used. Without the intention to detract in any way from their amazing value and spectacular and even life-saving effects under proper conditions and indications, it may nevertheless be truthfully stated that the final story of their morbidity and mortality has yet to be told. They carry with their use the real and frequent danger of edema, hypertension, heart failure, diabetes, perforation and massive hemorrhage of peptic ulcer, exacerbation of healed and latent tuberculosis and other infections, phlebothrombosis, psychosis, adrenal insufficiency and atrophy, and hypercortisonism; and many patients have died and are dying daily directly or indirectly from their use.[43, 44, 45, 46, 47, 48] The actual incidence of these serious and occasionally fatal effects is astronomically greater than the incidence of agranulocytosis from the use of aminopyrine.

In retrospect, of the six cases reported here, two were cases of acute exacerbation of rheumatic carditis (cases 1 and 3); one of ulcerative colitis and rheumatic heart disease (case 4); one of periarteritis nodosa (case 2),

and two of visceral (pancreatic) neoplasm (cases 5 and 6). It is in just such conditions, in which the antibiotics are not effective, that aminopyrine may be of particular value. In general, we have found its effect to be most striking in the virus, collagen, neoplastic and other nonbacterial diseases associated with fever. In bacterial infections, too, it is frequently effective in controlling fever and its associated symptoms, but it may fail in fulminant or terminal infections. Today, in all of these conditions corticotropin or the corticosteroids would no doubt be resorted to first; but these preparations are expensive and, as stated, not without considerable risk, and in some cases cannot be given because of a known contraindication to their use in a particular patient. In such circumstances, and in any case where fever per se is an essential problem, and the other metabolic and alterative effects of the corticosteroids are not particularly required, a preliminary trial of aminopyrine may be of value.

Summary

Six cases are reported to illustrate the potent antipyretic effect of aminopyrine. In three of these cases—one of periarteritis nodosa, and two of prolonged intractable fever of unknown origin but most likely due to acute exacerbation of rheumatic fever—aminopyrine was the only drug which controlled the fever and reversed the progressive downhill course of the disease, after weeks of ineffective therapy with large doses of chemotherapeutic and antibiotic agents. In these three cases the action of aminopyrine simulated that of a specific drug and proved to be life-saving. Agranulocytosis did not occur even in the cases where the drug was given over long periods of time (up to five months continually in two cases, and up to two years intermittently in another), and a tendency to leukopenia in one case was readily controlled by reduction in dosage. Aminopyrine is of value particularly in conditions not amenable to therapy with specific chemotherapeutic and antibiotic agents, or where these prove to be ineffective; in cases where other antipyretics are not tolerated or have failed; and in cases where one is unwilling to assume the risks of therapy with corticotropin and the corticosteroids, or these have failed, or some specific contraindication to their use exists in a particular case. However, aminopyrine may be used in any condition as the primary agent to control high or prolonged fever, alone, or as a supplement to other therapy.

Conclusion

Aminopyrine is still a uniquely valuable and occasionally life-saving antipyretic which deserves a trial whenever fever is a significant feature of the clinical picture of disease. It may be effective under conditions in which other antipyretics and even the most powerful and specific of the newer drugs fail. The danger of agranulocytosis from its use, although real, has been overemphasized and is no greater than with many other drugs

in common use today. Aminopyrine has its place in therapeutics under well controlled clinical conditions and under the supervision of a physician, but its careless and indiscriminate use is to be condemned.

SUMMARIO IN INTERLINGUA

Es reportate sex casos que illustra le potente effecto antipyretic de aminopyrina. In tres de iste casos—un de periarteritis nodose e duo de prolongate e debilitante febre de origine incognoscite (ben que probabilissimemente causate per exacerbationes acute de febre rheumatic e de carditis)—aminopyrina esseva le sol droga capace a regular le febre e a reverter le curso deteriorante del morbo post septimanas de therapia inefficace con grande doses de chimotherapeuticos, antibioticos, e altere agentes antipyretic. In iste tres casos le action de aminopyrina simulava le effectos de un droga specific e se provava como salva-vita pro le patientes. In le quarte caso—un caso de chronic morbo rheumatic del corde con stenosis mitral e exacerbation acute de chronic colitis ulcerative—aminopyrina sol regulava le febre de duration prolongate que previemente habeva essite refractori non solmente a agentes chimotherapeutic e antibiotic sed etiam a corticotropina. In le ultime duo casos—ambes con carcinoma pancreatic de forma multo avantiate—aminopyrina esseva de novo le sol agente capace a regular le prolongate febre e a contribuer assi transientemente al conforto e ben-esser del patientes. In iste casos, agranulocytosis non occurreva, mesmo quando le droga esseva usate durante longe periodos de tempore—usque a cinque menses continuemente in duo casos e usque a duo annos intermittentemente in un tertie. Un tendentia al disveloppamento de leucopenia in un caso esseva prestemente adjustate per un reduction del dosage.

Aminopyrina continua esser un antipyretico de valor incomparabile capace a salvar le vita del patiente in certe casos e digne de esser essayate quandocunque febre es un elemento significative in le tableau clinic del morbo. In certe respectos su action es analoge al potente effectos non-specific del corticosteroides e de corticotropina. Illo es de valor specialmente in conditiones de febrilitate que non pote esser tractate o que ha essite tractate sin successo per medio de un therapia a specific agentes chimotherapeutic e antibiotic (i.e. resistente infectiones bacterial; morbos virusal, collagenic, e metabolic; lymphomas; carcinomas; e forsan colpo de calor); in casos in que altere antipyreticos non es tolerate o ha essite usate sin successo; e in casos in que il non pare sage currer le riscos de un therapia a corticotropina e corticosteroide o in que iste agentes ha essite usate sin successo o in que il existe un specific contraindication individual que prohibi lor uso. Tamen, aminopyrina pote esser usate in omne situation como agente primari in le regulation de alte o prolongate febre—tanto per se como etiam in supplementation de un altere therapia. Le periculos que on associa con le uso de iste droga, specialmente le periculo de agranulocytosis, es real e non debe esser minuspreciate, sed illos representa non plus que un possibilitate distante. Illos es un cosa de idiosyncrasia personal plus tosto que un effecto del action pharmacologic del droga in general. Illos non excede le periculos de multe altere drogas que se trova in uso commun al tempore presente. Aminopyrina ha su placia in le therapeutica sub ben regulate conditiones clinic (frequente numerationes del sanguine) e sub le surveliantia de un medico, sed su uso incaute e indiscrete debe esser condemnate.

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NONTUBERCULOUS PNEUMONIA COMPLICATING PULMONARY TUBERCULOSIS *

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THE occurrence of nontuberculous pneumonia in patients with pulmonary tuberculosis still presents a problem in differential diagnosis. Its frequency remains disputed, and many clinicians are of the opinion that the coexistence of these diseases is rare. Prior to 1942 clinical reports of a few cases appeared in the literature, often with the opinion of the infrequent occurrence of the two diseases in the same patient.[1, 2, 3] In a recent publication on pneumonias, Reimann [4] states: "It is said that patients with pulmonary tuberculosis rarely get pneumonia caused by other bacteria, but the circumstance probably occurs more often than is believed." Previously, McPhedran [5] believed that he had identified chronic nontuberculous bronchopneumonias occurring in tuberculosis patients.

The first extensive report on this subject was a classic investigation published by Baum and Amberson in 1942.[6] They studied nontuberculous pulmonary infections complicating pulmonary tuberculosis. Among their cases were 102 cases of nontuberculous pneumonia, initially nonsuppurative, occurring in 97 patients treated on the wards of the tuberculosis service of Bellevue Hospital between 1932 and 1941. They considered the subject primarily from the viewpoint of the effect of the nontuberculous infection on the tuberculous process, the mechanism whereby the nontuberculous infection may cause activation of the tuberculosis, and the frequency of this activation. They include a thorough review of the earlier literature on the subject, including opinions of earlier German authors on the infrequent occurrence of the two diseases, and discussions of the mechanism of the influence of the two diseases on each other. Cases of nontuberculous infections related to bronchial distortion, neoplastic bronchial obstruction, or endobronchial tuberculosis, active or healed, were excluded from their study. The authors concluded that pneumonia was not rare in tuberculosis patients, and thought that the sheltered sanatorium life may have contributed to the previous reports of low incidence. However, they do not state the incidence that they observed.

In 1949 a follow-up report from Bellevue Hospital by Baum and Baum [7] added 155 cases of nontuberculous pneumonia occurring in patients with

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tuberculosis during the period from 1941 to 1947. Although one of their stated objectives was to present the actual incidence of complicating nontuberculous inflammations, they did not include these data. However, more cases were diagnosed at the Bellevue Hospital during this six-year period than during the previous nine-year period, and they concluded that the increased incidence of the diagnosis of the coexisting diseases was due to an increased awareness of the possibility rather than to an actual increase.

Baum and Amberson [6] proposed criteria for classifying activation of the tuberculosis by the nontuberculous infection as definite, probable, doubtful, none, and cases in which the activation was unknown because of insufficient data. In the first report from Bellevue there was an incidence of definite or probable activation in 18% of the total cases, and if the pneumonia occurred in a lobe involved by tuberculosis, activation occurred in 33% of the cases. A mortality of 17% occurred. In the second report from Bellevue, activation occurred in 24% of all pneumonias. If the two processes occurred in the same lobe, activation occurred in 49% of the total.

The authors believed that the presence of a necrotizing process in the pneumonia and its location in the same lobe as the tuberculosis are the most important factors in activation. They found that the nature of the original tuberculous lesion is of lesser importance, though activation was greater in more active tuberculous lesions than in fibrocalcific lesions and lesions successfully controlled by collapse therapy. In a small number of cases which were treated with sulfonamides and penicillin the incidence of activation was not reduced.

The only other large series of cases was reported by Hogan in 1945.[8] His cases were taken entirely from a review of the hospital records at the Philadelphia General Hospital from 1936 to 1944. Of 8,487 patients with tuberculosis during this period, he found 111 cases of pneumonia occurring in 104 patients, an incidence of 1.3%. Hogan considered this to be a startlingly low incidence, considering the prevalence of these two diseases, and it led him to consider the possibility of the existence of a bacterial antagonism between pneumonia and tuberculosis. There was an over-all mortality from the pneumonia of 38%, but among cases with active tuberculosis the mortality was 56%, so that the occurrence of pneumonia was often fatal.

Although Hogan reports an incidence of activation of approximately 15%, what this figure represents is not clear. From his data there was an incidence of definite or probable activation in 3.6% of all cases.

The objective of the present paper is to present our experience with this subject, including the manifestations and incidence of pneumonia in pulmonary tuberculosis, and problems arising in this era of antibiotics and antituberculosis chemotherapeutic agents. Our concern is mainly with the characteristics of the complicating pneumonia, rather than with the influence of the pneumonia on the tuberculosis.

Clinical Material

The cases comprising this report were obtained from patients admitted to the Public Health Service Hospital in Brooklyn, a 354-bed tuberculosis hospital. A total of 47 cases of nontuberculous pneumonia, occurring in 36 patients, were reviewed. The great majority of the patients are merchant seamen, among whom there is a high incidence of spree drinking and chronic alcoholism.

In order to study the incidence, two series were tabulated from among the total cases. The first series was obtained from the records of this hospital by a review of all cases discharged with the two coexisting diagnoses during the period of 1945 to June 30, 1954. In each case the charts and x-rays were reviewed by the authors, and those were discarded where the

Table 1

Computation of the Number of Patients with Tuberculosis Seen as In-Patients during the 1½-Year Period Comprising the Second Series of Cases, July 1, 1954, to January 12, 1956

Hospital Census on 6/30/54 (Not corrected for those not diagnosed TB)		331
New Admissions, 7/1/54 to 1/12/56	294	
(minus) No diagnosis of TB	11	
	283	283
Re-admissions, 7/1/54 to 1/12/56	229	
(minus) Already included under new admissions	47	
(minus) Already included in 6/30/54 census	101	
	81	81
Total patients studied during this period		695

diagnosis did not satisfy the clinical criteria. During this period, in which 2,074 patients were treated, a total of six cases occurring in six patients were retained in the series.

The second series consists of cases occurring in the one-and-one-half-year period from July 1, 1954, to January 12, 1956, in patients who were hospitalized at this facility during this period. A total of 41 cases in 30 patients were found. In this series nine of the cases occurred just prior to their transfer to this facility for continuous hospitalization, and the diagnosis of nontuberculous pneumonia and tuberculosis was made at the previous hospital or in retrospect by the authors in reviewing the past x-rays and clinical history of these patients. The authors were personally involved in 32 cases of this series. In order to tally an incidence of the occurrence of nontuberculous pneumonia in patients with pulmonary tuberculosis, it was computed that 695 individual patients with the diagnosis of pulmonary tuberculosis were hospitalized at this facility one or more times during this one-and-one-half-year period (table 1).

The criteria used to establish a diagnosis of nontuberculous pneumonia

were obtained by the following studies: (1) clinical signs and symptoms and laboratory studies; (2) response to specific treatment; (3) serial x-ray changes showing resolution of infiltration too rapid for tuberculosis. For our purpose it was assumed that it is unusual for a tuberculous infiltration, even with chemotherapy, to resolve almost completely before six weeks.

Those cases where the diagnosis of pneumonia was disputed and those where the pneumonia was secondary to neoplastic obstruction were discarded from the series. However, those cases where bronchial narrowing

TABLE 2

Status of the Tuberculosis Patients at the Time of Occurrence of the Pneumonia

X-Ray Extent of Tuberculosis		No. of Patients	
Minimal		2	
Moderate to far advanced		34	
Total Patients		36	
Activity of Tuberculosis		**No. of Cases**	**% of Cases**
Active		21	45
Inactive		26	55
Total Cases		47	100
Anti-Tuberculosis Chemotherapy Just Prior to Pneumonia		**No. of Cases**	**% of Cases**
No chemotherapy		32	68
Chemotherapy		15	32
Streptomycin and PAS	4		
Streptomycin and INAH	4		
INAH and PAS	3		
INAH alone	4		
Streptomycin, PAS and INAH	0		
Total Cases		47	100
Situation at Time of Occurrence of Pneumonia		**No. of Cases**	**% of Cases**
In-patient		13	28
Not hospitalized or in-patient on pass		34	72
Total Cases		47	100

or distortion was thought to be a predisposing factor in the pneumonia were admitted to the series and were considered to be among the significant examples. Where possible, bronchoscopic and bronchographic * studies were included.

OBSERVATIONS

The majority of the patients were in the 40 to 69 year age group. No women are included among these cases; only a few women patients are seen

* Some bronchograms were done with Visciodol, generously supplied by E. Fougera and Company, Inc., New York, N. Y.

TABLE 3

Major Symptoms of the Nontuberculous Pneumonia

	No. of Cases	% of Cases
Acute onset	37	79
Insidious onset	10	21
Fever	47	100
Chest pain	27	57
Chills	21	45
Increased cough	10	21
Rusty sputum	4	9
Herpes labialis or nasalis	3	6
Headache	3	6
Total Cases	47	

at this hospital. At the time of occurrence of the pneumonia only two of the patients had minimal tuberculosis, and 55% of the cases were considered inactive by criteria established by the National Tuberculosis Association. Sixty-eight per cent of the cases were not on antituberculosis chemotherapy prior to developing the pneumonia, and 72% were either on pass or not hospitalized at the time of developing the pneumonia (table 2).

Fever, chest pain and chills comprised the most frequent major symptoms (table 3). There was considered to be a febrile response in 100% of the cases, although in a few objective measurements were not adequate, and in some the temperature recordings were concluded to have been elevated on comparison with succeeding values.

Table 4 presents the x-ray description of the pneumonias. The description of a lobar pneumonia refers to consolidation of the major portion of an entire lobe, considering the superior segment of the lower lobes and the lingula to be anatomically distinct, as considered surgically. Lobular refers to consolidations involving less than the above, or to patchy involvement on x-ray. Some may prefer to call these localized bronchopneumonias. Certainly the differentiation is not clear-cut, and some authors, as Hogan,[8] do not attempt to separate lobar pneumonias from bronchopneumonias.

TABLE 4

X-Ray Appearance of the Nontuberculous Pneumonia

Classification of the Pneumonia	No. of Cases	% of Cases
Lobar	8	17
Lobular	26	55
Diffuse bronchopneumonia	13	28
Total cases	47	100

Location of the Localized Pneumonias	No. of Cases	% of Cases
Right upper lobe or upper division of left upper lobe	1	3
Middle lobe, lingula, and/or lower lobes	33	97
Total Cases	34	100

Among our cases, 55% presented a lobular or localized patchy x-ray appearance, and among the localized pneumonias 97% were in the lower portions of the lungs.

Of the 29 cases where sputum smears and cultures for pyogens were done, in only 10 could the diagnosis of pneumococcal pneumonia be made (table 5). Typing serum was not available during most of the study.* In 18 cases sputum cultures revealed alpha streptococcus, *Neisseria catarrhalis,* and *Micrococcus pyogenes,* usually mixed. These organisms, commonly found in the upper respiratory tract, have rarely been considered to be etiologic agents in pneumonia in adults. Probably in these cases the etiologic pathogen was not isolated, or may have been viral. The bacteriologic results, being in many cases inconclusive, do not appear suitable for generalizations.

TABLE 5

Sputum Studies for Etiologic Agent in Nontuberculous Pneumonia

Pneumococcus		10
Definite	8	
Probable	2	
Beta-hemolytic streptococcus		1
Mixed organisms (usually *Staph. aureus, Strep. viridans, N. catarrhalis*)		18
Total cases where sputum bacteriology was done		29

18 patients with studies of the tracheobronchial tree	Residual from pneumonia at 4 weeks	
	None	Some
No significant tracheobronchial abnormalities described	5	2
Some tracheobronchial abnormalities leading to or in the area of pneumonia	0	11
Total patients	5	13

In the second series, where the cases were gathered from personal observation and awareness, 30 patients with episodes of pneumonia among 695 individuals with tuberculosis that were seen in the hospital in a one-and-one-half-year period give an incidence of 4.3%. However, in the first series, where all the cases were assembled from the hospital records, six patients with pneumonia among 2,074 patients seen in the hospital give an incidence of less than 0.3%.

There were no deaths from the pneumonia. Using the criteria of activation employed by Baum and Amberson,[6] we found no definite activation of the pulmonary tuberculosis from the nontuberculous pneumonia. Probable activation occurred in one case, with the appearance of new infiltration following the pneumonia and in the same area. This patient was persistently sputum-positive at the time of the pneumonia, and had major tuberculous involvement of the same lobe but not the same segments. The degree of

* Pneumococcal typing serum was obtained through the courtesy of the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, N. Y.

activation was unknown in three cases where the status of the tuberculosis before the pneumonia was unknown. The tuberculosis was active after the pneumonia, but without progression. Thus, only one case of demonstrable activation occurred.

In table 5 there is a summary of 18 patients in whom bronchoscopy and/or bronchography was performed. The presence of residual densities at four weeks after the onset of the pneumonia, as indicated by the closest available x-rays, was employed to differentiate a normal rapid clearing from a delayed resolution. Baum and Amberson [6] and Cohen,[9] in considering the differential diagnosis of pneumonia versus tuberculosis, regarded a maximum to be three weeks for resolution of an uncomplicated pneumonia.

The tracheobronchial studies are incomplete and inconclusive. In many patients the examination followed the pneumonia, and some bronchial changes may have been due to the pneumonia. In only five cases was obstructive narrowing demonstrated leading to the area of the pneumonia, and the importance of other abnormalities of distortion is indefinite. Nevertheless, there is a suggestion of a relationship between the status of the tracheobronchial tree and the x-ray resolution of the pneumonia.

It would be difficult to present the entire 47 cases. However, to illustrate better the problems confronted by this subject, the following six cases are used as examples.

Case Reports

Case 1. A 52 year old white male was diagnosed as having active, moderately advanced cavitary tuberculosis of the left upper lobe in March, 1955. He was treated with streptomycin and PAS. By June his sputum had become negative on smear and culture, and x-rays continued to show progressive slow resolution. In September, 1955, he returned six days late from pass after heavy drinking. He had severe left lower chest pain, fever of 102.6° F. orally, shaking chills, rusty sputum, a leukocyte count of 26,600, with 76% segmented cells, 15% bands, and 6% lymphocytes. *Diplococcus pneumoniae* was present on smear and culture of sputum. Posteroanterior and left lateral x-rays of the chest showed complete consolidation of the superior segment of the left lower lobe. Penicillin was administered. The patient became afebrile and asymptomatic within 48 hours, and an x-ray three days after the initial film showed almost complete resolution of the pneumonia. Bronchography following this episode showed no abnormalities, and follow-up x-rays, sputum and gastric cultures showed no spread or reactivation of his tuberculosis.

Case 2. A 51 year old Chinese male had had almost continuous hospitalization from 1948 to 1953 for far advanced pulmonary tuberculosis. He was discharged in 1953 with inactive, bilateral fibrocalcific disease. One week prior to re-admission, on November 4, 1955, the patient had vague left chest pain, low grade fever and some nonproductive cough. A chest x-ray in the Outpatient Department revealed a new infiltration in the left lower lung field in the area of the lingula, and the patient was re-admitted. Physical findings were minimal, the leukocyte count was 13,100 with a normal differential, and sputum culture showed mixed organisms. He was started on penicillin and became asymptomatic within 48 hours. X-ray resolution began in two days, and by the twentieth day the major portion of the infiltration had cleared. Bronchoscopy showed marked deviation and distortion of the left main-stem bronchus, and bronchography showed lack of filling of the distal bronchioles of the

lingula following the pneumonia. Sputum and gastric examinations were persistently negative for tubercle bacilli. In this case a patch of insidious pneumonia may have been confused for a spread of tuberculosis in an inactive patient. Only by close follow-up was the differentiation confirmed avoiding months of unnecessary hospitalization and treatment.

Case 3. A 46 year old white male was diagnosed as having active, far advanced bilateral pulmonary tuberculosis in 1949. He was treated for four years with chemotherapy, with resulting residual cavitation of the right upper lobe, and positive sputa. In November, 1954, a lucite ball plombage of the right upper lobe was performed, but following the surgery his sputum remained positive. On June 9, 1954, the patient returned from pass after drinking heavily and gave a history of having been unconscious. He complained of right chest pain. Cyanosis and severe dyspnea were present. Although he had a fever of 102.4° F., the laboratory studies were not striking. The chest film showed dense infiltration in the right middle lobe and some in the lingula. The patient was placed on heavy broad-spectrum antibiotic treatment and remained critically ill, with remittent fever to 103° F. A chest film on June 24, 1955, showed an extensive increase in the density in the right lower lung field. Shortly following this he began to improve and to expectorate much dirty, yellow-green sputum. An x-ray on July 27, 1955, showed marked resolution of the infiltration, with a radiolucent outline in the right middle lobe. Follow-up x-rays showed continuing slow resolution, with some residual organized pneumonia and disappearance of the abscess. His chest films showed no spread of the tuberculosis, and his sputum and gastric cultures began to be reported negative shortly following this pneumonic episode. Bronchoscopy prior to his plombage had shown partial obstruction of the right intermediate bronchus, and marked narrowing of the right middle lobe bronchus to a slit. In this case aspiration pneumonia was complicated by suppuration and abscess formation. The relationship between resolution and poor drainage seems apparent. The possibility of tuberculous spread and cavitation was raised, but the subsequent course eliminated this.

Case 4. This case illustrates the diagnosis of pulmonary tuberculosis made concurrently with the diagnosis of pneumonia. A 51 year old white male was admitted to the hospital following an acute onset of chills, right chest pain, high fever and increased cough. He had bilateral apical infiltrates and a right middle lobe pneumonia on x-ray. At this time sputum studies also showed acid-fast bacilli. On penicillin there was dramatic clinical response, the patient becoming afebrile and asymptomatic within 48 hours. Although major x-ray resolution was at first rapid, continuing clearing was slower than is usually noted, but almost complete in one month. Bronchoscopy and bronchography showed no abnormalities, even though the final clearing had been retarded.

Case 5. A 62 year old white male had long-standing, far advanced cavitary disease with such extensive fibrosis and severe ventilatory insufficiency that he required almost continuous nasal oxygen and bed-rest. The routine three-month chest film, taken on September 21, 1955, revealed a new left lower lobe infiltration. On investigation it was found that the oral temperature readings taken routinely from September 21 to 24 showed a low grade temperature elevation to 99.6° F. (orally), attributed at the time by his physician to his tuberculosis. At that time the patient had increased shortness of breath and chest pain, and the only antibiotics he was receiving were PAS and INAH. When the possibility of pneumonia was presented he was started on penicillin, later changed to erythromycin on the basis of sensitivity studies, but resolution was slow. The patient not only had a poor cough reflex but also was receiving codeine daily. He was encouraged to avoid the codeine and, following this, cough and expectoration increased, with good resolution of the pneumonia. This case emphasizes the dependency of diagnosis upon awareness, the commonly

recognized unreliability of oral temperatures in patients who are hyperventilating, and the ill effects of codeine in depressing a useful cough mechanism.

Case 6. A 50 year old white male had a history of tuberculosis dating back to 1946. A left pneumonectomy had been performed in 1948 and was followed by a spread to the right upper lobe. On antituberculous chemotherapy the patient became inactive and was discharged fit for light duty in 1954. He had pneumococcal pneumonia in 1950, and in February, 1955, and was transferred to this hospital following the second episode. Pulmonary function studies showed moderately severe ventilatory insufficiency, and the patient was maintained on domiciliary care. In

TABLE 6

Comparison of Series

Dates of Study	Baum and Amberson 1932–1941	Baum and Baum 1941–1947	Hogan 1936–1944	Manhattan Beach PHS Hospital	
				1945–June 30, 1954	July 1, 1954–Jan. 12, 1956
No. of patients with TB studied	Not stated	Not stated	8,487	2,074	695
No. of cases of non-TB pneumonia and % incidence	102 Not stated	155 Not stated	111 (111/8,487) 1.3%	6 (6/2,074) 0.3%	41 (41/695) 5.9%
No. of patients with non-TB pn. and % incidence	97 Not stated	Not stated	104 (104/8,487) 1.2%	6 (6/2,074) 0.3%	30 (30/695) 4.3%
Source of cases: a. hospital records b. personal observation	Combined, figures not stated	Not stated, probably combined	111 0	6 0	9* 32
Activity of TB a. Active b. Inactive	Not stated	Not stated	29% 71%	33% 67%	44 % 66%
Activation of TB by non-TB pneumonia†	18%	24%	3.6%	0	1 case 2.4%
Deaths from the pneumonia	17 (17%)	Not stated	42 (38%)	0	0

* Cases in which pneumonia occurred at another hospital just prior to admission. Some of these not diagnosed initially but in retrospect by the authors.

† Definite or probable activation according to criteria of Baum and Amberson (tabulated as cases per total cases of pneumonia).

October, 1955, he had an acute episode of dyspnea, right chest pain, cyanosis, and a fever of 103.4° F. His sputum showed pneumococci, the leukocyte count was 16,300, with 53% segmental cells and 40% bands. A diffuse bronchopneumonia was apparent on x-ray. The patient was acutely ill and 10 hours after the onset went into shock, which was relieved by norepinephrine. He was started on penicillin, isopropylarterenol inhalation, and oxygen. There was a prompt clinical response, and his temperature fell to 100° F. rectally, continuing as a low grade fever for four days. By the fourteenth day there was rapid x-ray resolution of the infiltration in the right lower lobe but persistence in the upper lobe. This, however, also cleared five days later. Previous bronchoscopy had revealed marked deviation of the trachea to the

right, with rotation and deviation of the right main-stem bronchus. In this case the added insult of pneumonia to a poorly functioning lung made the situation critical. Only prompt diagnosis and vigorous treatment prevented a fatality.

Discussion

Table 6 presents a comparison of our series with those of the authors referred to above. Between our two series there is a large difference in the incidence of nontuberculous pneumonia in pulmonary tuberculosis. This illustrates how a study of past hospital record diagnoses, as in Hogan's study, may be misleading. An awareness of the possibility of the diagnosis and its significance will lead to its more frequent confirmation and better documentation. It also seems reasonable that an episode of pneumonia during the course of several years of hospitalization for tuberculosis may easily be overlooked when the final diagnoses are being recorded on discharge. We are inclined to agree with Baum and Baum [7] that the incidence of the concurrent diagnoses increases with awareness. The fact that two thirds of our cases were not in the hospital at the time of occurrence of their pneumonia appears consistent with the suggestion of Baum and Amberson [6] that a sheltered sanatorium life may contribute to a lowered incidence of pneumonia.

A low incidence of demonstrable reactivation of the tuberculosis by the pneumonia is apparent in these cases in which almost half were active. Since the occurrence of the pneumonia and tuberculosis in the same lobe was not tabulated, and since the large majority of the pneumonias occurred in the lower portions of the lung, it may be that a lack of location of the diseases in the same area is a factor in the low activation. However, the extent of involvement by the tuberculosis at some time in its course is frequently much greater than the location of the major amount of disease discernible on x-ray, and it would be difficult to determine accurately the possible locations of dormant tuberculous foci. Undoubtedly, also, the evaluation of activation will vary with the investigator in spite of common criteria.

In contrast to the other series, most of our cases occurred during an era of effective antituberculosis drugs and potent antibiotics. It appears reasonable that more effective treatment of the tuberculosis and the pneumonia was important in preventing activation.

The relationship of the status of the tracheobronchial tree and the resolution of pneumonia has been observed by others.[4, 6] Obstruction to an effective bronchial drainage may be not only a stenotic narrowing but may also be a distorted trachea or bronchus inhibiting an effective cough. Chronic tuberculous patients with consequent bronchial abnormalities will be more susceptible to development and prolongation of pneumonia after surgical procedures or other predisposing situations.

Most of the cases presented do not demonstrate the classic picture of a lobar pneumonia. The x-ray densities are often patchy and the clinical course is frequently insidious. Many pneumonias will be missed if one

waits for the typical lobar pneumonia. Chronic nontuberculous pulmonary infections are being frequently described and they may easily simulate tuberculosis.[10] They may occur in cases of tuberculosis as well.

Only a few of our cases presented the problem of diagnosing a concurrent tuberculosis at the time of the pneumonia in a patient without a previous diagnosis of tuberculosis. In a patient with known tuberculosis, there may be a tendency to think of a new x-ray density with mild symptoms in terms of a spread or reactivation. To a patient with inactive tuberculosis this may cost months of unnecessary treatment with our present concept of long-term chemotherapy. If the possibility of pneumonia is not considered and the diagnosis aided by frequent serial x-rays, the differential diagnosis of a new patchy infiltration may remain in doubt. In patients who have been inactive, observation on antibiotics without antituberculosis drugs may aid in the differentiation.

At the present time, with medication and surgery better able to arrest the tuberculous disease, more patients with extensive pulmonary involvement will survive. They will be left with a damaged bronchial system and limited pulmonary reserve. In these patients, the occurrence of pneumonia may be life-threatening in spite of antibiotics.

Summary

This report presents the characteristics of 47 cases of nontuberculous pneumonia occurring in 36 patients with pulmonary tuberculosis. The results are compared with previous series presented in the literature, all covering the era before antituberculosis chemotherapy and before the newer antibiotics were available. In the present study the absence of mortality from the pneumonia and the low incidence of exacerbation of the tuberculosis by the pneumonia contrast with the earlier series. Of these cases studied, nontuberculous pneumonia occurred in 4.3% of 695 tuberculosis patients treated during a one-and-one-half-year period while under the personal observation of the authors. Yet an examination of the records at this hospital revealed a substantiated pneumonia listed among the final discharge diagnoses in only 0.3% of 2,074 patients treated in the previous 10-year period. Few of the pneumonias presented the picture of a classic lobar pneumonia, and it is concluded that the incidence of the combined diagnoses rose with awareness. A relationship between the status of the tracheobronchial tree and resolution of the pneumonia is tentatively suggested by bronchoscopic and bronchographic examinations. Emphasis is given to the importance to the patient of making the correct diagnosis and the effect on ventilatory insufficiency of the pneumonia in an already damaged lung.

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SUMMARIO IN INTERLINGUA

Iste reporto presenta le characteristicas de 52 casos de pneumonia non-tuberculotic occurrente in 38 patientes con tuberculose pulmonar. Le resultatos es comparate con simile series presentate previemente in le litteratura. Illos omnes pertine al periodo ante le introduction de chimotherapia antituberculotic e del plus recente antibioticos. In le presente studio le absentia de mortalitate ab pneumonia e le basse incidentia de exacerbation del tuberculose per le pneumonia forma un frappante contrasto con le previe series. Inter le casos studiate, pneumonia non-tuberculotic occurreva in 4,3% de 695 patientes tuberculotic qui esseva tractate in le curso de un periodo de un anno e medie sub le observation personal del autor. Nonobstante, le scrutinio del archivos de iste hospital revelava le documentate representation de pneumonia inter le diagnoses listate al tempore del dimission final in solmente 0,3% del 2.074 patientes tractate in le curso del precedente periodo de 10 annos. Esseva pauco numerose le casos de pneumonia exhibiente le tableau de classic pneumonia lobar, e le conclusion es formulate que le incidentia del combinate diagnose se augmenta con le attention que es prestate a illo. Un relation inter le stato del arbore tracheobronchial e le resolution del pneumonia es proponite tentativemente super le base de examines bronchoscopic e bronchographic. Es sublineate le importantia—pro le patiente—de establir le correcte diagnose e le effecto que le pneumonia exerce super le insufficientia ventilatori de un jam lesionate pulmon.

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CLINICAL STAFF CONFERENCE

PRIMARY ALDOSTERONISM: CLINICAL STAFF CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH *

Participants: FREDERIC C. BARTTER, M.D., and EDWARD G. BIGLIERI, M.D.,
Bethesda, Maryland

DR. FREDERIC C. BARTTER: The diagnosis of primary aldosteronism is suggested by the findings of hypertension, hypokalemia and alkalosis.

The chemical abnormalities result from the continuous autonomous overproduction of aldosterone, resulting in excessive excretion of hydrogen and potassium ions, presumably exchanged for sodium ions by renal tubular cells. As potassium depletion ensues, (1) urinary ammonia excretion increases, and the urine may become alkaline despite continued excessive hydrogen excretion, (2) the ability to produce a concentrated urine, even with exogenous pitressin, may be lost, with resultant relative water loss and hypernatremia, (3) further renal damage may result in nitrogen retention and failure of sodium conservation, and finally, (4) aldosterone secretion may be depressed as a result of potassium depletion, further obscuring the diagnosis.

"Salt-losing nephritis" constitutes the greatest problem in differential diagnosis. Here, obligatory renal sodium loss may lead to secondary increases in aldosterone secretion, and this in turn leads to alkalosis, hypokalemia, potassium depletion, loss of concentrating ability, and, finally, *hyper*natremia, exactly as with primary aldosteronism.

We believe that the response to use of a very low sodium diet provides not only a valuable adjunct to treatment but also the most useful available information with regard to differential diagnosis. With a low sodium diet the following occurs:

1. Patients with both primary and secondary aldosteronism are enabled to retain potassium much better than they can with high sodium diets. (This is true presumably because, on low sodium diets, less sodium reaches the distal tubular site where hydrogen and potassium ions are secreted. The corollary is that when *no* sodium is reaching this site, as with cardiac failure, even very large amounts of aldosterone will not produce alkalosis or potassium loss.)
2. Patients with primary aldosteronism and little or no renal damage may immediately demonstrate the ability to lower urinary sodium virtually to zero, thus ruling out a primary tubular sodium-losing lesion.

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Requests for reprints should be addressed to Charles G. Zubrod, M.D., National Institutes of Health, Bethesda 14, Maryland.

3. Patients with primary aldosteronism and considerable renal damage who have lost the capacity for renal sodium conservation may, after restoration of the potassium deficit, demonstrate a return of this aspect of renal function.

We have two cases† to present. Both presented with hypertension and hypokalemic alkalosis, and were studied for primary aldosteronism. Dr. Edward Biglieri will present the clinical findings.

DR. EDWARD G. BIGLIERI: *Case 1.* A 13 year old white schoolboy was referred to the Clinical Center because of hypertension in July, 1955. Aside from polydipsia and nocturia "as long as he could remember," his health had been excellent until January, 1954, when he experienced the sudden onset of a 10-day febrile illness, with temperatures to 105° F. and mild pharyngitis. Although poliomyelitis was suspected, the diagnosis could not be established. Hypertension was noted for the first time during that illness.

During the summer of 1954 the patient was hospitalized elsewhere for investigation. Chest x-ray revealed no cardiomegaly, and an intravenous urogram was normal. The electrocardiogram was characteristic of hypokalemia. Serum sodium values of 151, 147 and 148 mEq./L., with corresponding serum potassium values of 1.9, 2.2 and 1.8 mEq./L., were recorded.

The Fishberg concentration test showed maximal specific gravity to 1.010, and pitressin was said to produce no further increase. Sixty per cent of phenolsulfonphthalein dye appeared in one hour. A Regitine test was negative, but urinary catechols were "very high" on two occasions.

On September 29, 1954, a bilateral adrenal surgical exploration for pheochromocytoma was performed. No adrenal tumor was found, nor was any tumor observed along the course of the sympathetic trunks. The adrenal biopsy showed normal cortex. The renal biopsy revealed disease of small vessels described as arteriolar sclerosis and focal thrombonecrosis, either primary or secondary to hypertension. The patient was subsequently discharged on combinations of Ansolysen, Apresoline and Raudixin, which controlled the hypertension temporarily. Follow-up urinary catechols were normal.

On admission to the Clinical Center, the patient was a well developed and well nourished 14 year old boy in no distress. The blood pressure was 160/120 mm. of Hg in both arms and 200/150 mm. of Hg in both legs. The only other abnormal physical finding was hypertensive retinopathy, Grade I (generalized narrowing and some tortuosity of retinal arterioles).

Chest x-ray showed no cardiomegaly, and intravenous urograms were normal. The electrocardiogram was suggestive of left ventricular hypertrophy, with abnormal ST-T waves and a QT interval at the upper limits of normal. Chemical analyses shortly after admission gave the following serum concentrations: sodium, 148–152 mEq./L.; carbon dioxide content, 32 mEq./L.; chloride, 105 mEq./L., and potassium, 3.0 mEq./L. Serum creatinine was 1.1 mg. %. Repeated Fishberg concentration tests showed maximal specific gravity response to 1.014, and no further increase could be produced with pitressin. Sixty-three per cent of phenolsulfonphthalein dye was excreted in one hour. Urinary catechols were normal. An eight-hour intravenous infusion of ACTH (50 units) produced a

† These cases were reported briefly in discussion of Garrod, O.: Primary aldosteronism, Symposium on aldosterone, Ciba Foundation, 1957, Churchill, Ltd., London.

rise in urinary 17-hydroxycorticoids from 5.5 to 19.2 mg. per 24 hours. Eosinophils decreased from 133 to 19 per cubic millimeter. The first urinary aldosterone value, obtained on a high sodium diet, was 18 μcg. per 24 hours, but the next three were 5 μcg. per 24 hours.

The essential features of the hospital course, during which numerous studies were done, are shown in figure 1, to which we shall return in a moment. In brief, we studied his response to low and high sodium intakes and to low and high potassium intakes, and then performed an operation.

Case 2. A 27 year old white man was referred to the Clinical Center because of persistent hypertension of one year's known duration. When first measured during this illness, his blood pressure was 260/160 mm. of Hg. It had been normal three years before.

A hospital examination six months before admission revealed no cardiomegaly on chest x-ray, normal intravenous urogram, an electrocardiogram suggestive of left ventricular hypertrophy, and maximal concentration on the Fishberg test to 1.010. The patient was placed on various combinations of Ansolysen, Apresoline and Serpasil. An attempt was made at moderate sodium restriction.

He had noted occipital headaches, polydipsia and polyuria for about one year before the hypertension was first noted.

On admission the patient was a lean, well developed 27 year old man in no distress. Physical examination was normal except for a blood pressure of 260/160 mm. of Hg in both arms, and Grade I hypertensive retinopathy.

The electrocardiogram showed left ventricular hypertrophy and left ventricular strain. An intravenous urogram showed downward displacement of the right kidney by a calcified adrenal mass (figure 1). Serum electrolyte concentrations on two occasions were: sodium, 147 and 149 mEq./L.; potassium, 2.6 and 2.4 mEq./L.; carbon dioxide content, 33 and 36 mEq./L., and chloride, 101 and 102 mEq./L. The Regitine test (5 mg. intravenous) was negative, and urinary catechols were within the normal range (88 μcg./24 hours). During an eight-hour intravenous infusion of ACTH (40 units), the serum 17-hydroxycorticoids rose from 19 to 23 mcg. %, and urinary 17-hydroxycorticoids from 5.8 to 11.1 mg. per 24 hours (both responses below normal for this laboratory), but the eosinophils decreased from 218 to 26 per cubic millimeter. When water was withheld for 24 hours, urine osmolarity rose to only 535 mm./Kg. H_2O, indicating marked impairment of concentrating ability. Inulin clearance was 108 c.c./min. Two urinary aldosterone values on a normal diet with 250 mEq. of added sodium were 39 and 41 mcg./24 hours. (On this sodium intake, aldosterone levels below 10 mcg./24 hours are normally found.)

One month after initial admission the patient was brought in for further studies. These studies are shown in part in figure 2. In brief, we studied his response to high and low sodium intakes, and to hydrocortisone, and then performed an operation.

Before we tell you the operative findings, Dr. Bartter will discuss the studies that were done.

DR. FREDERIC C. BARTTER: Case 1 (figure 2) had been explored surgically a year before, and no adrenal tumor had been found. Thus, even with the triad of hypertension, hypokalemia and alkalosis, and the initial finding of elevated aldosterone excretion on a high sodium intake, we hesitated to make a diagnosis

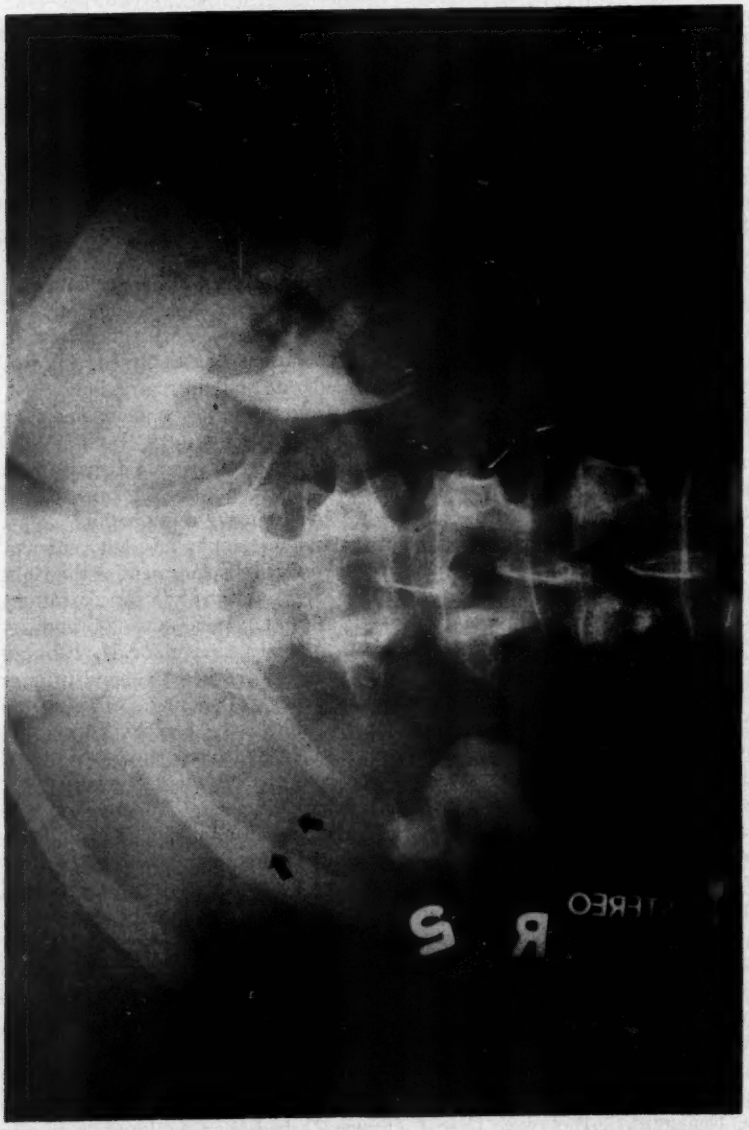

FIG. 1. Intravenous urogram showing downward displacement of the right kidney and calcium deposits at site of right adrenal adenoma.

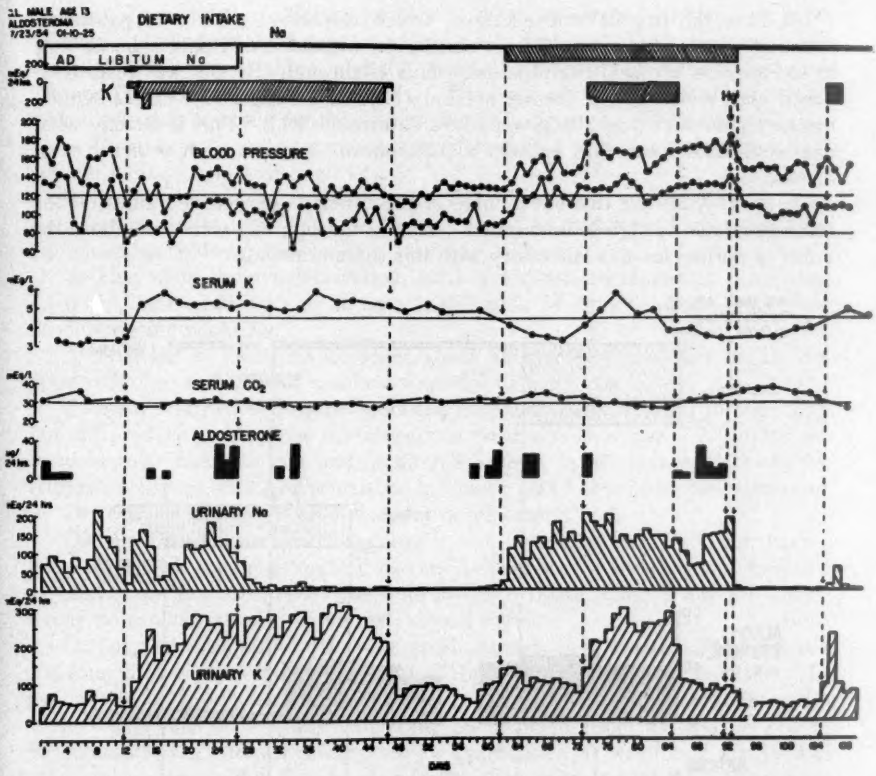

FIG. 2. Blood pressure and metabolic data on case 1. (For discussion, see text.)

of primary aldosteronism. When the three subsequent aldosterone values were normal we were given further pause.

Over the next four months, however, the studies shown in figure 2 (q.v.) convinced us that he did have primary aldosteronism. These studies showed:

1. That upon "loading" with potassium, urinary aldosterone values rose appreciably (days 12 through 26). This is what might have been anticipated if the early low values had been a "result" of potassium depletion.*

2. That upon sodium deprivation, urinary sodium fell almost to zero, albeit over a 14- instead of the normal four- to five-day period (days 27 through 62). This effectively ruled out "sodium-losing nephritis" as the cause of his metabolic difficulties.

3. That upon sodium deprivation urinary aldosterone did not rise, but continued to fluctuate between 12 and 33 micrograms a day (days 27 through 62). This is what might have been anticipated if the adrenal secretion of aldosterone were autonomous, and not subject to normal control.

* In a number of normal subjects we have found that potassium depletion consistently lowers aldosterone excretion.

4. That the hypokalemic alkalosis, which responded readily to potassium "loading" (day 12 et seq.), did not recur even without added potassium as long as sodium was withheld from the diet (days 47 through 62), but was readily induced with restoration of dietary sodium (days 63 through 92), unless supplementary potassium was also given (days 73 through 84). This is exactly what one would anticipate with primary aldosteronism,[1] and not with primary renal disease.

5. Finally, all but two out of nine of the urinary aldosterone values on the second regimen of high sodium intake (days 62 through 92) were well above the limits of normal for this laboratory with this sodium intake.

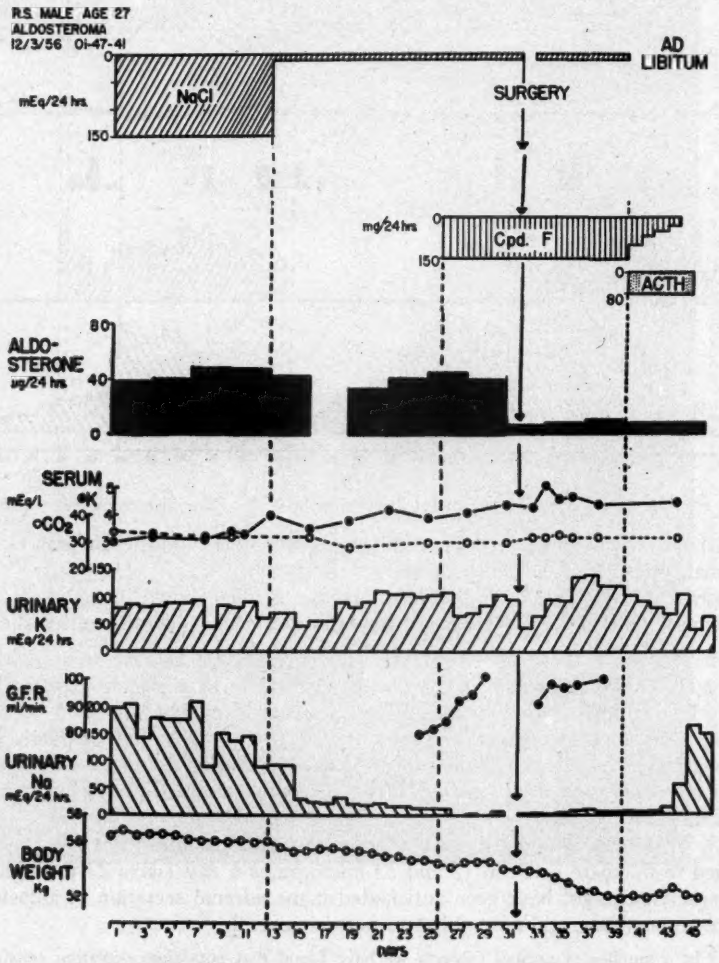

FIG. 3. Metabolic data on case 2. (For discussion, see text.)

Case 2 presented a different problem. Whereas severe hypertension, hypokalemia and alkalosis were present when he was first seen, the hypertension was mild (180/100 mm. of Hg), and the chemical abnormalities were almost gone (figure 3) when he came in for studies. The diagnosis of primary aldosteronism was supported, however, by the studies shown in figure 3. They showed:

1. That urinary aldosterone excretion remained very high despite a high sodium intake (days 1 through 12).

2. That urinary aldosterone excretion did not increase upon sodium deprivation despite weight loss (days 13 through 30). As with case 1, this suggested "autonomous" aldosterone secretion.

3. That upon sodium deprivation, urinary sodium fell almost to zero (days 13 through 31), although, as in case 1, this took 14 days to occur—ruling out "sodium-losing nephritis."

4. That the hypokalemic alkalosis, albeit mild when the studies began, disappeared when sodium was withheld from the diet.

5. Also, that hydrocortisone produced no natriuresis (days 26 through 31), but did produce a sharp rise in endogenous creatinine clearance. A similar rise of glomerular filtration rate and of filtered sodium "load" may explain the natriuresis observed with hydrocortisone in Conn's case [2] of primary aldosteronism.

Dr. Biglieri will tell us of subsequent developments.

DR. EDWARD G. BIGLIERI: Because it was clear that case 1 did not have a large tumor, we sought to make it as easy as possible for the surgeons to find a small one: we gave delta-1-9-alpha-fluorohydrocortisone, 2 mg. a day for several weeks, to produce atrophy of normal adrenal tissue.

On surgical exploration, two very small adrenals were found. The right one and four fifths of the left were removed. They were histologically normal. The patient's blood pressure fell to 120/80 mm. of Hg, and urinary aldosterone fell to very low values. He was sent home on no medication and did very well. Seven months later he was re-admitted for evaluation. It was found that he was completely normal clinically and chemically when receiving 20 mEq. of sodium a day, would become hypertensive when the sodium intake was increased, and acutely hypotensive when it was reduced. A standard dose of ACTH intravenously produced clearly subnormal responses in urinary and plasma 17-hydroxycorticoids (from 6 to 14 mg. per day, and from 12 to 25 μcg. % respectively). Urine concentration rose normally in response to pitressin.

Case 2 was explored surgically and an adrenocortical adenoma, 6 cm. in diameter, was removed, together with the adherent right adrenal. The tumor showed numerous flecks of calcification, areas of necrosis and areas of hemorrhage, and an intact capsule. A renal biopsy was normal.

Urinary pH, which had ranged from 7.01 to 7.31 before surgery, fell promptly to 5.89 to 6.84. The blood pressure fell gradually, reaching normal levels in a week; it is still normal six months later. The patient is completely normal, clinically and chemically.

DR. FREDERIC C. BARTTER: In summary, we believe both patients had "primary" aldosteronism, in case 1, as a result of hyperplasia, in case 2 as a result of aldosteroma. Case 1 bears a striking resemblance to one reported by Holten and Posborg Petersen.[3] In both cases the syndrome was preceded by an obscure febrile illness affecting the central nervous system. This raises the question as

to whether a lesion in the central nervous system can lead to aldosterone production. In both cases, sodium restriction was effective, both as an aid to diagnosis (in ruling out primary renal disease), and as an aid to therapy (in relieving the hypokalemic alkalosis).

SUMMARIO IN INTERLINGUA

Le diagnose differential de aldosteronismo primari es discutite. Le autores crede que un proba a restriction de natrium es le plus importante mesura diagnostic, proque illo servi a excluder nephritis con perdita de natrium e rende possibile le restauration del kalium del corpore.

Es reportate studios effectuate in duo patientes con hypertension, hypokalemia, e alcalosis. Ambes habeva dysfunction renal, con hypernatremia e incapacitate de producer urina concentrate. In ambes, numerose essayos de aldosterona urinari monstrava valores supranormal que non esseva influentiate per alterationes in le ingestion de natrium. In ambes, le excretion urinari de natrium deveniva negligibile con le restriction del natrium, e alora le alcalosis hypokalemic esseva facilemente alleviate. Adrenalectomia subtotal in le un e ablation de un tumor adrenal in le altere esseva sequite per le disparition de omne anormalitates. Le aldosterona urinari habeva descendite a basse valores.

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CASE REPORTS

GASTROINTESTINAL COMPLICATIONS OF COLCHICINE THERAPY IN GOUT *

By EDWARD SHANBROM, M.D.,† *Duarte, California,* and LEONARD RAPOPORT, M.D., *Milford, Connecticut*

COLCHICINE has a long and venerable history in the treatment of gouty arthritis, and even now is generally considered the drug of choice for this disease. Since it has been used for gouty arthritis since the fifteenth century, it is not surprising that its pharmacology has been intensively studied and its toxic manifestations have been well described. It is the purpose of this paper to review the gastrointestinal complications associated with colchicine therapy, and to present two cases observed at surgery in which certain unusual lesions were observed which may have been produced by colchicine.

Poisoning due to colchicine produces a rather characteristic clinical picture.[1, 2, 3, 4] The symptoms for the most part arise from the gastrointestinal tract, even when it is given parenterally, for the excretion of colchicine is by the alimentary tract. Typically, an interval of several hours elapses between the administration of the drug and the onset of symptoms. These begin with pharyngeal burning, increased salivation, nausea, dysphagia and abdominal pain, and proceed to severe vomiting, colic, diarrhea and tenesmus. At the start the stools may be normal, but they then become mucoid and bloody. With progression of this dysentery phase the clinical picture resembles that of cholera, with the patient evidencing exhaustion, collapse, and progressive muscular paralysis. Postmortem examination in these instances reveals marked inflammation of the gastrointestinal tract.

When colchicine is employed in the treatment of gout it is common to induce some mild degree of gastrointestinal irritation, even though only small amounts of the drug are administered. Hyperemia of the stomach and intestines and hemorrhagic gastroenteritis have been noted even after hypodermic administration.[1]

Since the pharmacologic actions of colchicine have been well detailed in the literature, and since its documented use extends over a considerable period of time, one would anticipate a plethora of reports in the literature on pathologic lesions of the gastrointestinal tract induced by colchicine administration. Surprisingly, however, there is a paucity of such recorded observations. Davis and

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Bartfeld,[5] in their discussion of the intravenous use of colchicine, referred to a case of their own and to one of Talbott's in which the administration of an intravenous colchicine-iodide-salicylate preparation led to gastrointestinal hemorrhage. (This latter case was not confirmed in personal communication with Dr. Talbott.) Talbott and Gutman,[6] who have each had vast experience with colchicine, state that they have never encountered pathologic changes in the gut due to the use of this drug. While the proof of a cause-and-effect relationship between colchicine administration and gastrointestinal lesions is necessarily a tenuous one, the occurrence of two cases within a few months in whom such a relationship seems plausible and in whom lesions were observed at surgical exploration has prompted this report.

Case Reports

Case 1. This 36 year old white male lumber salesman entered the hospital with the complaint of intermittent epigastric pain and melena of 24 hours' duration. The patient had a one-year history of peptic ulcer, with a good response to conservative management. He was known to have had gouty arthritis for 11 years, with four or five severe attacks each year and minor attacks every few months. There was a familial history of gout (the patient's father and three brothers). A renal calculus, presumably of a uric acid nature, had been passed by the patient in 1951. Attacks involving both great toes, ankles and wrists had been treated at various times in the past with colchicine and phenylbutazone.

Admission physical examination revealed only slight pallor. There was no evidence of arthritis at this time. All admission laboratory studies were within normal limits except for a hematocrit of 40%. Conservative management of the ulcer symptoms was initiated, but on the third hospital day there was a sudden drop in the hematocrit. The patient was transfused with 3,000 c.c. of blood. Emergency gastrointestinal series revealed a duodenal ulcer. The patient improved and was asymptomatic until the tenth hospital day, when he developed bilateral ankle pain. Colchicine, 0.5 mg., was administered every six hours. Because of some mild gastrointestinal discomfort and nausea following the first two oral doses, colchicine was administered in intravenous form, three doses of colchicine-salicylate-iodide preparation being administered in the next 18 hours. On the twelfth hospital day the patient had a sudden onset of right flank pain, radiating anteriorly to the right upper quadrant of the abdomen. Marked agitation of the patient was noted, but there was no change in the vital signs or elevation of the white blood count. Urinalysis showed no red or white blood cells. X-rays revealed no free air under the diaphragm, and an intravenous pyelogram was normal. Serum amylase values were normal. The pain persisted and became more severe, and the patient was accordingly transferred to the surgical service, where an exploratory laparotomy was performed. During surgery, examination of the abdominal organs revealed moderate edema of the duodenum but no other abnormalities of the stomach, liver, gall-bladder, pancreas or kidneys. While the surgeon was running down the bowel it was noted that even minimal handling traumatized the mesentery and produced fresh subserosal hemorrhage. It was also noted that there were linear hemorrhages on the bowel wall, extending along the mesenteric vessels in areas that had not been previously handled by the surgeon. The omentum appeared granular, with reddened papillary projections. A biopsy of omentum was taken, the appendix was removed and the abdomen was closed. The postoperative course was marred by atelectasis and pneumonitis, but the patient recovered rapidly and was discharged on the seventh postoperative day.

Pathologic Report: Gross examination: The first specimen was an appendix 5.5 cm. in length and 6 mm. in diameter. The serosa was congested and bloodstained,

and fatty mesentery was attached. The lumen contained bloodstained mucus. The mucosa was pink and glistening. The second specimen was a piece of adipose membrane, apparently omentum, 6.5 by 4.5 cm. and 3 to 6 cm. thick. It was bloodstained, and several small, focal, fresh hemorrhages had occurred into the fatty lobules. Microscopic: Sections of the omentum showed congested adipose tissue into which numerous hemorrhages had occurred. There was no inflammation or fat necrosis. Section of the appendix revealed no inflammatory changes.

Case 2. This 68 year old white male jewelry salesman had a long history of acute and chronic tophaceous gouty arthritis, with innumerable attacks affecting ankles, knees, toes, fingers, wrists and elbows. The attacks of arthritis were treated with colchicine, 0.5 mg. every hour until relieved. In June, 1953, the patient noted rectal bleeding while hospitalized for pneumonia, and this was attributed to "one of the medications." The patient's complaints of anorexia and weight loss, reinforced by x-ray reports of a constricting lesion of the rectosigmoid, prompted sigmoidoscopy and surgical exploration. At surgery diffuse inflammatory lesions of the bowel were found, with adherence of the ileum to the rectosigmoid and fistulization. Biopsies were taken of the rectosigmoid, the ileum and of a fistula site, and a resection of the ileum with an end-to-end anastomosis and transverse colostomy was performed.

Pathological Report: Gross: The specimen consisted of a 58 cm. resected ileum with attached mesentery. The upper portion was normal. The lower 15 cm. of ileum showed edema, congestion, fibrosis of the wall, adhesion between loops and on the serosal surface, acute and chronic gray-brown purulent exudate. This likewise involved the mesentery at this point. There was no evidence of tumor. Microscopic: Section of ileum showed normal mucosa, considerable edema and congestion of the submucosa, acute and chronic inflammatory infiltration of the muscularis, and a dense acute and chronic inflammation of the serosa. On the serosal surface was a fibrinopurulent exudate. Biopsy findings were not considered compatible with the diagnosis of regional enteritis.

Following the exploration in 1953 the patient had a closure of his transverse colostomy and creation of a sigmoid loop colostomy because of the rapid transit time of food and resulting cachexia. Repeated sigmoidoscopy biopsies and biopsies at surgery revealed only granulation tissue with chronic inflammation like that initially observed.

Discussion

The first case is unique in that the onset of acute symptoms prompted surgical exploration only a few hours after the patient had been receiving colchicine. Whether the picture of an acute abdomen can be readily ascribed to the diffuse gastrointestinal and mesenteric hemorrhages cannot be answered. What is important, however, is that the opportunity arose for us to examine the viscera of a patient who had been taking colchicine. The ecchymotic areas were remarkable to visualize—not one of the several physicians present at surgery had ever witnessed such lesions. The hemorrhages for the most part seemed to fan out along the mesenteric vessels as they emerged from the intestines, but a smaller number of bleeding areas were also seen in the subserosal layer of the intestinal wall, particularly on its mesenteric surface. The whole picture suggested specific irritation of the bowel wall and its blood vessels, caused by the absorption of some toxic agent.

The question then arose as to whether these lesions could be attributed specifically to colchicine. Although it is true that the patient had received intravenous colchicine in combination with iodide and salicylate, this preparation had

been stopped two days before the operation. We feel that the time interval was sufficient to rule out the possibility of iodide or salicylate sensitivity, as has been suggested by Davis and Bartfeld.[5] It seems reasonable, then, to assume that colchicine itself was the noxious agent, since it was the only drug being administered until the sudden onset of abdominal pain. There is actually very little else that could have caused the pathologic changes. The possibility of a blood dyscrasia was considered, but adequate hematologic investigation eliminated this idea. Microscopic examination of mesenteric tissue containing hemorrhage which was removed at surgery failed to reveal any specific cellular infiltrative changes.

Finally, the picture we observed at surgery so closely resembled that which has been described in poisoning due to colchicine, as outlined in the beginning of this paper, that it seemed justifiable at least to consider strongly that colchicine caused the gastrointestinal bleeding tendency in our patient.

The mechanism by which colchicine produces gastrointestinal hemorrhages is not well understood. Boyland and Boyland [7] showed that there is a reduction in the ascorbic acid content of intestinal tissue following colchicine administration, which results in local tissue scurvy. That vitamin C deficiency might have played a role in our patient is a most appealing concept, since his milk-alkali diet contained no vitamin supplement and he was therefore deprived of ascorbic acid in his diet for 12 days.

The implication that the inflammatory changes in the second case were due to colchicine would appear to be on less solid ground, and obviously it is impossible for us to establish a distinct cause-and-effect here. However, some inferences can be drawn from what was observed at surgery and from the tissue changes observed under the microscope. As was true of the hemorrhages seen in the first case, the inflammatory lesions in this second case were widely distributed throughout the bowel and the mesentery, and were so situated along the course of the mesenteric vessels as to suggest a relationship to absorption from the gastrointestinal tract. Microscopic examination of a section of diseased ileum showed acute and chronic inflammatory infiltration of the muscularis and mucosa. A fibrinopurulent exudate was present on the serosal surface. Cultures of various types had failed to reveal any specific causative agent. We feel, too, that enough time has elapsed in a follow-up of this case to allow the development of other changes which might suggest the diagnosis of a more specific disease process, but this has not occurred. In his history the patient had not been exposed to any known toxic gastrointestinal substance, with the exception of prolonged colchicine administration.

Experimentally, there is a little evidence to suggest that colchicine might produce such a picture. Although it is very well known that colchicine may retard cell growth by stopping mitosis in metaphase, it is not generally mentioned that this drug is also capable of stimulating specific cellular proliferation. However, the drug has been used in the laboratory to produce hyperplasia of leukocytes, histiocytes, fibrocytes and epithelial cells. Musotto and Diquattro [8] showed that they could induce proliferation of histiocytes with a tendency towards epithelioid formation in various organs of guinea pigs, including the intestinal tract, by small doses of colchicine. The observation by Lits [9] that masses of chromatin are excreted from the intestines and other organs of colchicine-treated mice is pertinent, since the presence of both stimulation and destruction may result in hypertrophy

or atrophy of tissue. The work of the Belgian school on the cytotoxicology of colchicine has been summarized by Lits, Kirschbaum and Strong,[10] establishing that early or late mitotic hyperactivity can be seen in various tissues, including the blood and the digestive tract.

Conclusions

Although it is obvious that we cannot state categorically that colchicine was the agent responsible for the pathologic lesions described in our two patients, it is not unreasonable to assume that such is the case. The fact that colchicine has been shown to produce similar lesions experimentally favors this concept. That such toxic manifestations have not been reported before in gouty patients receiving tiny doses of colchicine may simply be because surgical intervention at the opportune time to observe such changes would be rare. Our first patient was operated on because of suspected complications of a duodenal ulcer. It is quite likely that if he had experienced the abdominal pain outside the hospital while routinely taking colchicine for an attack of gout, we would merely have attributed the griping pain to colchicine therapy and would not have considered him a surgical candidate.

It is hoped that the presentation of these cases will stimulate others to search for similar changes in patients receiving colchicine.

Summary

1. The clinical picture of colchicine poisoning is briefly discussed.

2. Two cases of gastrointestinal complications associated with colchicine therapy in gouty subjects are presented. The first case exhibited diffuse hemorrhages of the subserosal layer of the intestines and the mesentery, while the second case showed diffuse inflammatory changes of the abdominal viscera.

3. Experimental data from the literature are reviewed which suggest that colchicine is capable of producing these pathologic changes.

Summario in Interlingua

Ben que colchicina es in uso in le tractamento de gutta depost multe annos, il existe solmente pauchissime reportos de complicationes gastrointestinal occurrente post su ingestion. Duo casos esseva observate al exploration chirurgic in le quales il pareva plausibile supponer que le administration de colchicina esseva responsabile pro producer specific lesiones gastrointestinal.

Le prime patiente esseva un juvene masculo blanc, admittite al hospital pro le tractamento de un acute sanguinante ulcere peptic. Durante su hospitalisation, ille requireva moderate quantitates de colchicina pro combatter attaccos de acute arthritis guttose. Le dece-secunde die—durante un curso multo normal de restablimento ab le symptomas del ulcere—ille disveloppava le aspectos clinic de un abdomine acute. Un laparotomia exploratori revelava hemorrhagias subserosal del intestino e mesenterio. Le omento presentava un apparentia granular con rubificate projectiones papillar. Esseva trovate nulle altere causa pro le signos e symptomas del abdomine acute.

Le secunde patiente esseva un masculo blanc de 68 annos de etate qui depost multe annos prendeva colchicina pro chronic gutta tophacee. Ille esseva admittite al hospital a causa de manifestationes clinic compatibile con un lesion obstructive del intestino crasse. Un intervention chirurgic esseva effectuate, e diffuse lesiones

inflammatori del intestino esseva trovate, con adherentia del ileo al rectosigmoide. Le biopsia de iste lesiones produceva resultatos que non esseva considerate como compatibile con le diagnose de enteritis regional sed plus tosto con un diagnose de un chronic e non-specific processo inflammatori. Subsequentemente plure biopsias esseva effectuate tanto al tempore del intervention chirurgic como etiam de examines sigmoidoscopic, sed le constatationes microscopic esseva semper le mesmes.

In ambe iste casos, le location del lesiones suggereva le occurrentia de un irritation specific del pariete intestinal e de su vasos sanguinee mesenteric per le absorption de un agente toxic. Nihil in le historias del duo patientes poteva attribuer le responsabilitate pro iste lesiones a un altere agente noxiose. Meticulose studios clinic e laboratorial, insimul con un longe periodo de observationes consecutori, non revelava ulle altere mechanismo o processo pathologic que poteva esser considerate como responsabile pro le presentia del lesiones observate. Es discutite le mechanismos per que colchicina produce possibilemente tal lesiones gastrointestinal.

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HYPERTROPHIC OSTEOARTHROPATHY IN ASSOCIATION WITH CONGENITAL CYANOTIC HEART DISEASE: REPORT OF TWO CASES*

By Robert W. Trever, M.D., *Baltimore, Maryland*

The association of simple clubbing of the fingers and toes with congenital cyanotic heart disease is a well known phenomenon. The association of congenital cyanotic heart disease and hypertrophic osteoarthropathy is not so well recognized. The following cases are of significant interest in this regard.

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Case Reports

Case 1. A 17 year old white schoolboy was admitted to the hospital on March 19, 1956, complaining of swelling and pain in his ankles and knees. He had been cyanotic from the time of birth. His mother had been told that he was "a blue baby" and that nothing could be done for him.

At age six months the patient had had pneumonia. At age two years he had had a draining ear for six months. He did not enter school until age eight, and had attended school only sporadically because of exertional dyspnea and frequent upper respiratory infections. He was in the eighth grade at the time of admission to the hospital.

The patient had never been observed to squat. At age 12 he had been seen in the Harriet Lane Home of the Johns Hopkins Hospital. It was thought at that time that he had either a Taussig-Bing syndrome or an atypical Eisenmenger's complex. Fluoroscopy revealed huge pulmonary arteries with a hilar dance. He had no joint symptoms, and the only abnormal finding in the skeletal system was the marked clubbing of the fingers and toes. He was generally underdeveloped.

In October, 1955, the patient began to have aching, swelling and tenderness of his ankles. His ankles were sometimes too sore to touch. His knees became similarly involved, and he occasionally noted some swelling of his wrists. His weight fell from 85 to 75 pounds between October, 1955, and March, 1956. He felt feverish intermittently.

Three weeks before admission to this hospital the patient was seen by a local physician, who instituted digitalis therapy. The patient's mother had previously given him aspirin intermittently, with some relief of the joint pains.

Temperature was 100.0° F.; pulse, 80; respirations, 20; blood pressure, 104/70 mm. of Hg in both arms. The patient was an underdeveloped boy who appeared closer to 10 than to his stated age of 17 years. He was alert, oriented and coöperative. His emotional development seemed more appropriate to his apparent than to his actual age, but his mentality seemed normal. There was deep cyanosis, especially of the lips and nail-beds. Mucous membranes appeared plethoric as well as cyanotic. The retinal veins were engorged and displayed increased tortuosity. The disc margins were indistinct. There was a retinal shimmer. The gums were hypertrophied. The tonsils were large. No râles were heard over the lung fields. He was able to lie flat without discomfort. There was a precordial heave. A systolic thrill was palpable over the precordium. A pulmonic tap was palpable. The left border of cardiac dullness percussed 10.5 cm. from the midsternal line in the seventh and eighth interspaces. There was a somewhat rough, short, grade 4 systolic murmur over the entire precordium, maximal in the third and fourth interspaces along the left sternal border. The murmur could be heard faintly in the left interscapular region. The pulmonic second sound was markedly accentuated. Hepatic dullness extended from the sixth interspace to 5 cm. below the right costal margin in the midclavicular line. The spleen was not palpable. Pubic and axillary hair were almost absent. The testes were small. There was marked clubbing of the fingers and toes. Bilateral patellar clicks could be elicited, and there was swelling about the knees and ankles. There was no pedal or pretibial edema. There was slightly increased heat about the knees. The joints were not painful on manipulation. Neurologic examination was not remarkable.

Hematocrit was 71.5. White blood cell count was 9,050, with a normal differential. Urinalysis was normal except for the presence of rare red cells. Electrocardiogram showed a right ventricular strain pattern. C-reactive protein complement fixation titer was 3000. Antistreptolysin O titer was 333 Todd units. Hemostatic function studies were normal. Three blood cultures were sterile.

Chest fluoroscopy revealed ventricular enlargement, the right ventricle appearing most prominent. There was no apparent atrial enlargement. The pulmonary arteries were enormous (figure 1).

X-rays of the long bones showed periosteal elevation and new bone formation along the lower thirds of both tibiae and fibulae. There was periosteal elevation, with laminated new bone formation along the distal three quarters of the ulnar bones (figures 2 and 3).

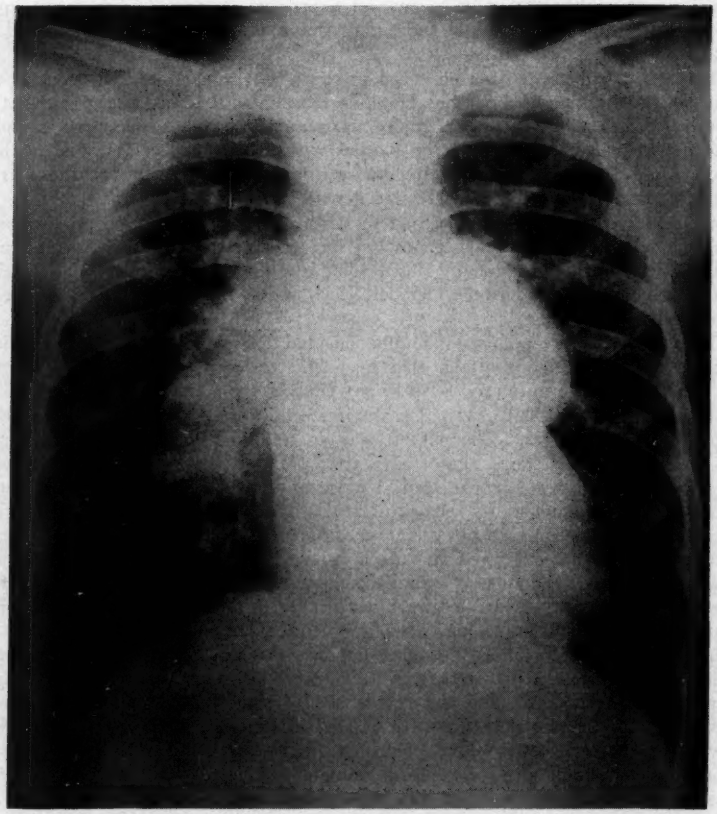

FIG. 1. *Case 1.* Chest film, demonstrating cardiac enlargement and enormous pulmonary arteries.

The patient was seen in consultation by Dr. Helen Taussig, who made the diagnosis of transposition of the great vessels with an interventricular defect. She agreed that the patient had hypertrophic osteoarthropathy. She stated that there was no satisfactory surgical procedure for improving his cardiovascular function.

The patient was discharged on a program of maintenance digitoxin, a 4 gm. salt diet, and aspirin for symptomatic relief of his joint pains.

Case 2. A 43 year old Italian-born white housewife was admitted to the hospital on November 12, 1956, complaining of pains in her joints. She had been cyanotic

since infancy, and had noted clubbing of her fingers for as long as she could remember. She had always suffered from mild exertional dyspnea.

For about 25 years the patient had been troubled by intermittent episodes of pain in her wrists, knees and ankles. For 10 to 15 years these episodes had been more severe, and associated with swelling about the involved joints. During this time there had been slowly progressive enlargement of these joints.

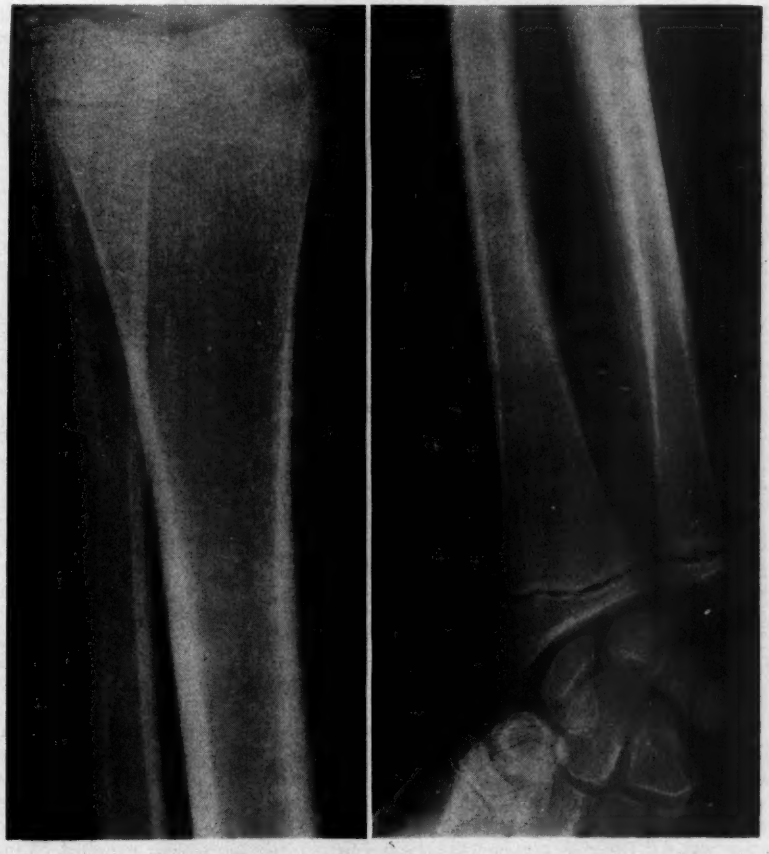

FIG. 2 (left). *Case 1.* X-ray of tibia and fibula, showing periosteal elevation and new bone formation.

FIG. 3 (right). *Case 1.* X-ray of the radius and ulna, demonstrating periosteal elevation with laminated new bone formation.

In 1952 digitalis therapy was instituted because of persistent swelling of the ankles and gradual weight gain.

For two years the patient's main complaints had centered about her joints. Serum uric acid was found to be 6.4 mg.%, but therapy with colchicine and probenecid produced no improvement. For six months she had become progressively incapacitated by joint symptoms.

Temperature was 99.0° F.; pulse, 70; respirations, 16; blood pressure, 95/70 mm. of Hg. She was a short, dark-skinned woman with obvious cyanosis and plethora. The retinal veins were engorged. No râles were heard over the lung fields. The heart was not enlarged. There was a slight precordial heave. A grade 3 systolic murmur, maximal in the pulmonic region and radiating over the precordium, was heard. The pulmonic second sound was slightly decreased in intensity. The cardiac rhythm was regular. There was no hepatomegaly. Striking clubbing of the fingers and toes was evident. There was enlargement of the wrists and ankles (figure 4). There were pain on motion and increased warmth about the left wrist. There was some tenderness over the long bones.

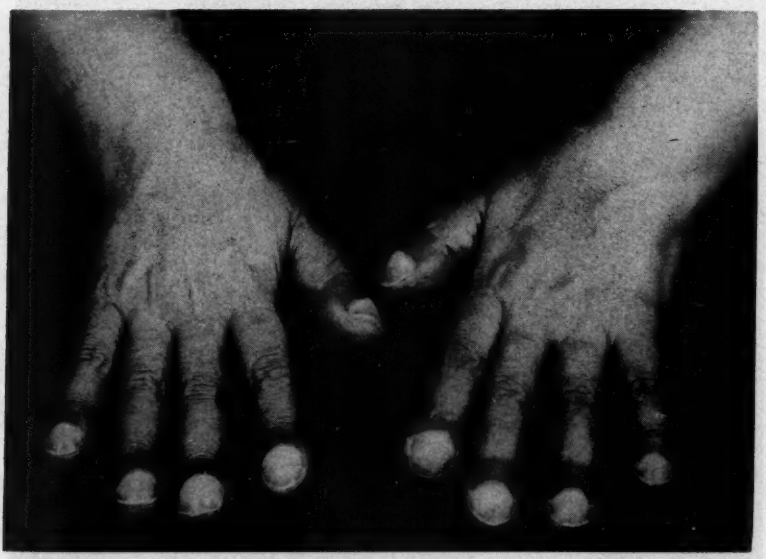

FIG. 4. *Case 2.* Photograph of the hands, demonstrating striking clubbing of the fingers and enlargement of the wrists.

Hematocrit was 72. White blood cell count was 5,200, with a normal differential. Urinalysis showed a trace of protein. Nonprotein nitrogen was 57 mg. %. Total protein was 6.7 gm. %, with 4.1 gm. albumin and 2.6 gm. globulin. Uric acid was 10.4 mg. % on one determination and 8.0 mg. % on another. Calcium levels were 12.9, 13.4 and 12.8 mg. %. Phosphorus was 5.6 mg. %, and alkaline phosphatase was 4.0 Bodansky units. On a low calcium diet the patient excreted 52 mg. of calcium in a 24-hour urine specimen.

Chest fluoroscopy revealed no cardiac enlargement. The pulmonary segment was somewhat concave. The pulmonary vascular markings were diminished, with decreased hilar pulsations. A triangular density in the right cardiophrenic angle had been present for a number of years and was felt to represent either an epicardial fat pad or an accessory lobe.

The electrocardiogram showed a right ventricular strain pattern. Cardiac catheterization findings were compatible with pulmonary stenosis, ventricular septal defect, left superior and inferior venae cavae, and an anomalous pulmonary vein entering the right atrium.

X-rays of the skeletal system revealed periosteal reaction along the shafts of the long bones, reaction being particularly marked in their distal portions (figure 5). Similar reaction was seen in the metacarpal bones, the patellae and the right clavicle. These changes had the typical characteristics of hypertrophic osteoarthropathy.

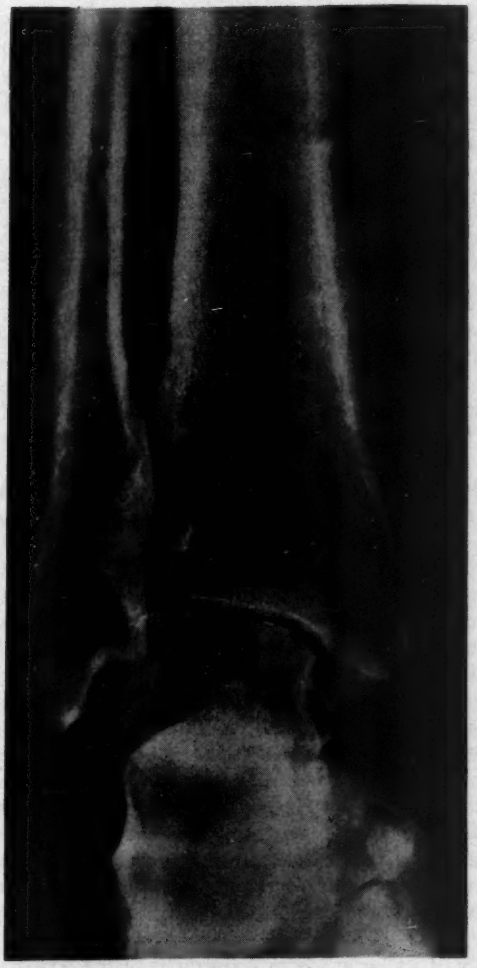

FIG. 5. *Case 2.* X-ray of tibia and fibula, showing extensive periosteal reaction.

Surgical intervention was not thought advisable for the management of the patient's congenital heart disease. She was continued on her cardiac regimen and kept at bed-rest. She was begun on 0.2 mg. atropine subcutaneously every six hours. There was evidence of satisfactory atropinization. On this program she experienced marked relief of her joint symptoms. Substitution of placebo injections for a 24-hour period did not alter this improvement.

Discussion

The first patient had long-standing clubbing in association with congenital cyanotic heart disease. For six months he had suffered from arthralgias and swelling involving the knees, ankles and wrists. At the time of admission there was evidence of fluid in the knee joints and periarticular swelling involving both the knees and ankles. X-rays showed periosteal elevations and new bone formation along the distal portions of both tibiae and fibulae, as well as both ulnae. This patient obviously suffered from hypertrophic osteoarthropathy. No evidence could be demonstrated of any cause for this, other than his underlying congenital cyanotic heart disease.

The second patient also presented characteristic findings of hypertrophic osteoarthropathy in association with congenital cyanotic heart disease. In addition, this patient had hyperuricemia and hypercalcemia without hypercalciuria. She demonstrated none of the changes of gouty arthritis. The hypercalcemia was unexplained. It was not felt that these latter findings had any bearing on the hypertrophic osteoarthropathy.

The subjective response of the second patient to atropine was of interest in view of the recent work of Flavell. He has reported five cases of bronchogenic carcinoma (four of which were unresectable) associated with hypertrophic osteoarthropathy in whom the vagus nerve was surgically severed on the side of the affected lung. This resulted in prompt relief of the persistent pain of osteoarthropathy in all five cases.[1]

In a recent discussion of the diagnostic significance of clubbing Vogl et al. state that they were unable to find records of patients in whom periosteal or synovial changes developed after stationary asymptomatic clubbing had been present for years. They comment further that they are unaware of such an occurrence in uncomplicated congenital cyanotic heart disease.[2]

Mendlowitz, in a review of the subject of clubbing and hypertrophic osteoarthropathy, has taken an opposite view, stating that hypertrophic osteoarthropathy can be found in any condition with which clubbing is associated, including congenital cyanotic heart disease.[3] In support of this he refers to a case reported from the University College Hospital in London in 1907.[4] The patient was a 21 year old woman who had suffered from cyanosis and dyspnea since birth. She had a systolic murmur maximal in the third and fourth interspaces along the left sternal border. She had had pains in her ankles and wrists and the long bones of her legs for 10 years. She had marked clubbing of the fingers and toes. X-rays demonstrated enlargement of the tibiae and fibulae, especially in their lower portions, and of the upper portions of the shafts of the femora. The patient was stated to be free of any signs or symptoms of pulmonary disease.

More recently (1947) Means and Brown reported a case of a 26 year old male with tetralogy of Fallot in whom deformities of the wrists and ankles were first noted at the age of 12. He had had periodic pains in his wrists and ankles in adolescence. He was moderately cyanotic, and had marked clubbing of his fingers and toes and soft irregular swellings about the wrists and ankles. X-rays of the tibiae and fibulae showed productive periosteal changes in their distal portions. The distal portions of the radius and ulna showed increased diameter, and soft tissue swelling was evident. The patient underwent operation, an anastomosis being established between the right common carotid and the right

pulmonary arteries. It was necessary to resect the right subclavian artery, but circulation in the right arm proved adequate. Within six weeks the deformities about the hands and feet were less conspicuous, the improvement being especially noticeable in the right hand.[5]

In a series of over 3,000 cases of congenital cyanotic heart disease seen at the Harriet Lane Home of this hospital, only three patients with associated hypertrophic osteoarthropathy have been encountered.[6] These were the two cases being reported and that of Means and Brown who underwent operation at this hospital. This adds further emphasis to the low frequency of the association. None of the reported cases has developed symptoms or signs of hypertrophic osteoarthropathy earlier than the age of 11 years.

Experimentally, a similar situation has been produced in the dog. Mendlowitz and Leslie were able to establish a permanent fistula between the pulmonary artery and the left auricle in four dogs, reproducing the type of circulatory derangement found in congenital cyanotic heart disease. One of these animals developed hypertrophic osteoarthropathy. This dog was sacrificed eight months postoperatively (the other animals died four, four and 11 months postoperatively). X-rays of the radius and ulna of the dog in question showed periosteal proliferation. The presence of periosteal new bone formation was confirmed at autopsy by both gross examination and microscopic section of the long bones.[7]

Summary

Two cases have been presented of congenital cyanotic heart disease with long-standing clubbing and the characteristic findings of hypertrophic osteoarthropathy. A review of the American and British literature revealed only two other well documented similar cases. Thus, although simple clubbing of the fingers and toes is a common associated feature of congenital cyanotic heart disease, hypertrophic osteoarthropathy is quite unusual.

Acknowledgments

The author wishes to express his thanks to Dr. Frank Standaert, Dr. Wil B. Nelp and Dr. Michael Criley, who participated in the care of these patients, and to Dr. Helen Taussig, Dr. R. C. Tilghman and Dr. Richard Johns for their helpful suggestions.

Summario in Interlingua

Le association de simple digitos hippocratic del manos e pedes con congenite morbo cardiac cyanotic es un ben-congnoscite phenomeno. Le association de congenite morbo cardiac cyanotic con osteoarthropathia hypertrophic es minus recognoscite.

Es presentate le casos de duo patientes con congenite morbo cardiac cyanotic, digitos hippocratic de longe durantia, e le constatationes characteristic de osteoarthropathia hypertrophic. Le secunde del duo patientes experientiava un melioration subjective durante un programma de injectiones de atrópina. Iste observation esseva de interesse con respecto a un recente reporto per Flavell concernente cinque patientes con carcinoma bronchogene (non-resecabile in quatro) e osteoarthropathia hypertrophic in qui le nervo vage esseva dissecate chirurgicamente al latere del pulmon afficite. Omne le cinque patientes experientiava un prompte alleviamento del dolores osteoarthropathic post le effectuation de iste manovra.

Un revista del litteratura de lingua anglese revelava solmente duo altere reportate casos de congenite morbo cardiac cyanotic in association con osteoarthropathia hyper-

trophic (per contrasto con simple digitos hippocratic). In un de iste duo casos, le alterationes ossee e articular regredeva post le establimento chirurgic de un derivation inter le carotica dextere e le arteria dextero-pulmonar.

Un simile association ha essite producite per medios experimental. Mendlowitz e Leslie effectuava un fistula permanente inter le arteria pulmonar e le auriculo dextere de quatro canes, e un de iste animales disveloppava osteoarthropathia hypertrophic.

Le association de osteoarthropathia hypertrophic con congenite morbo cardiac cyanotic es de bassissime frequentia. In un serie de plus que 3.000 patientes con congenite morbo cardiac cyanotic, vidite al clinica pediatrico-cardiac de iste hospital, solmente tres tal casos esseva incontrate.

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LÖFFLER'S SYNDROME: REPORT OF A CASE ASSOCIATED WITH ADMINISTRATION OF MEPHENESIN CARBAMATE (TOLSERAM) *

By Theodore Rodman, M.D., William Fraimow, M.D., and Ralph M. Myerson, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

In 1932 and 1936 Löffler [1, 2] described a syndrome, commonly associated with his name, characterized by transitory pulmonary infiltrations that are often migratory, eosinophilia, and a benign course with few symptoms. Since then experimental, clinical and pathologic evidence has been accumulated which supports the allergic nature of this syndrome. A wide variety of agents have been incriminated as allergens. Many reports describe Löffler's syndrome secondary to various helminthic infestations. Less frequently, cases have been reported in association with amebiasis,[3] brucellosis,[4] coccidioidomycosis,[5] and following

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exposure to ragweed and privet pollen.[6] The administration of drugs such as Prontosil,[7] sulfonamides,[8, 9] penicillin [10, 11] and para-aminosalicylic [12, 13] has been followed by the development of Löffler's syndrome. Frequently, a definite allergen cannot be identified.

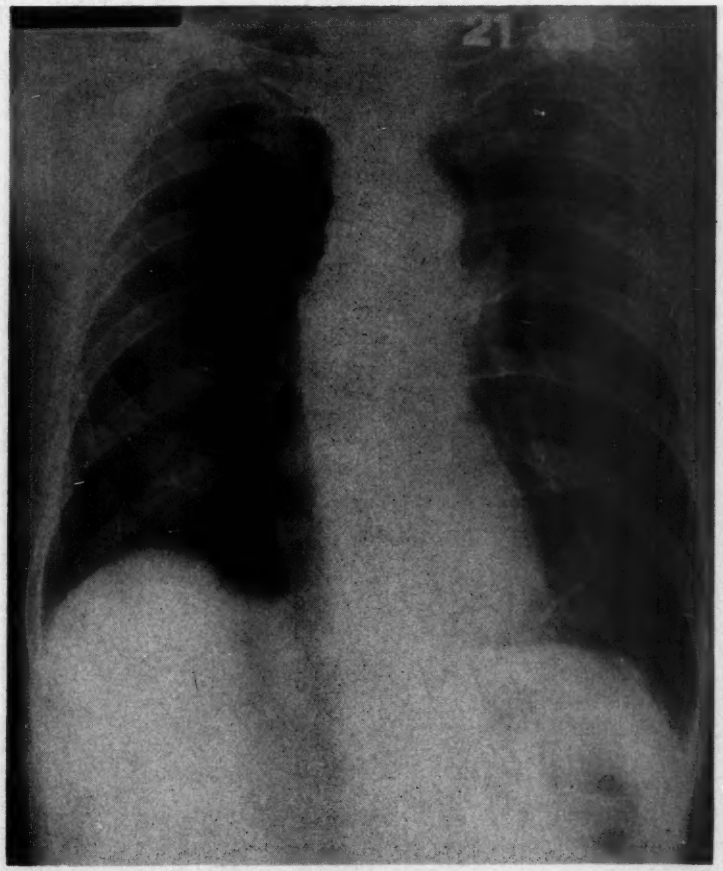

FIG. 1. Roentgenographic appearance of the patient's chest on admission to the hospital.

The following case is of interest in that a clinical picture compatible with Löffler's syndrome occurred during therapy with mephenesin carbamate (Tolseram), and recurred after each of three subsequent brief administrations of this drug. As far as can be determined, no similar reaction to Tolseram has been reported.

CASE REPORT

A 77 year old white man was admitted to the Veterans Administration Hospital, Philadelphia, July 21, 1955. He had a long history of frequency of urination, noc-

turia and chronic low back pain. In the month prior to admission, back pain had become severe and hospitalization was recommended. The patient had had a transurethral prostatectomy in 1948, with little improvement in his urinary complaints.

Physical examination was within normal limits except for straightening of the lumbar spine, tenderness to percussion over the third lumbar vertebra, and spasm of the paravertebral musculature. The prostate gland felt normal to digital examina-

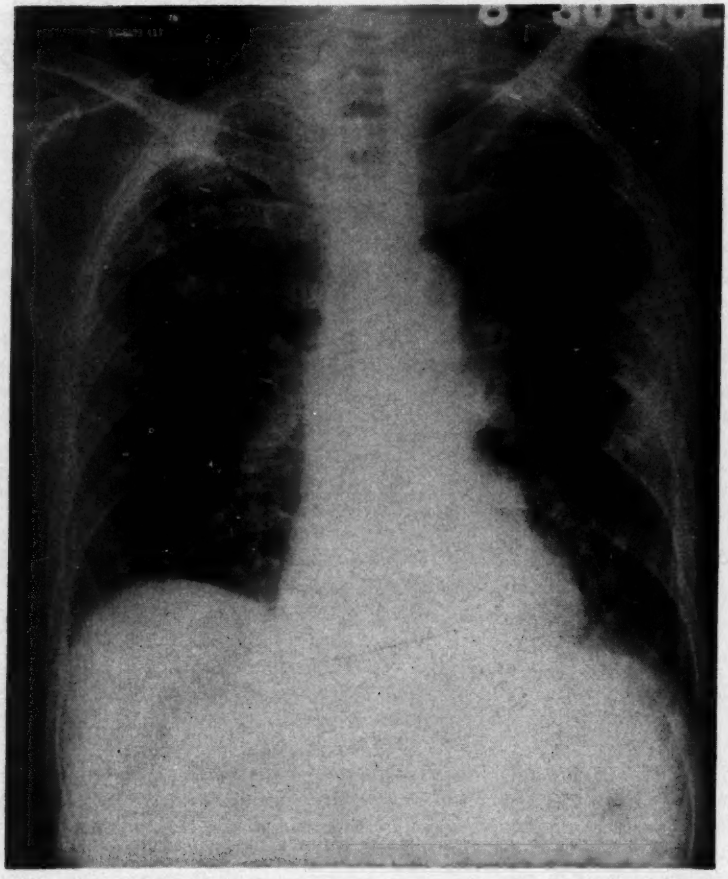

FIG. 2. Roentgenographic appearance of the chest at the height of the reaction.

tion. Roentgenograms revealed a normal chest (figure 1), extensive osteoporosis of the lumbar spine and a compression fracture of the third lumbar vertebra.

The hemogram was normal. The initial leukocyte count was 5,500 per cubic millimeter, with 2% eosinophils. Urinalysis revealed a moderate degree of pyuria due to alpha-hemolytic staphylococci. Except for a blood urea nitrogen of 36 mg. per 100 ml., blood chemistries were within normal limits. Investigative procedures to determine the cause of the osteoporosis were unrewarding. Serum proteins, cal-

cium, phosphorus, acid and alkaline phosphatase values were within normal limits. There was no demonstrable evidence of multiple myeloma or primary or metastatic bone tumor.

The patient was treated with physiotherapy and, on his fifth hospital day was placed on mephenesin carbamate (Tolseram), 4 gm. daily, in an attempt to alleviate pain and spasm. In addition to Tolseram, the patient received a course of procaine

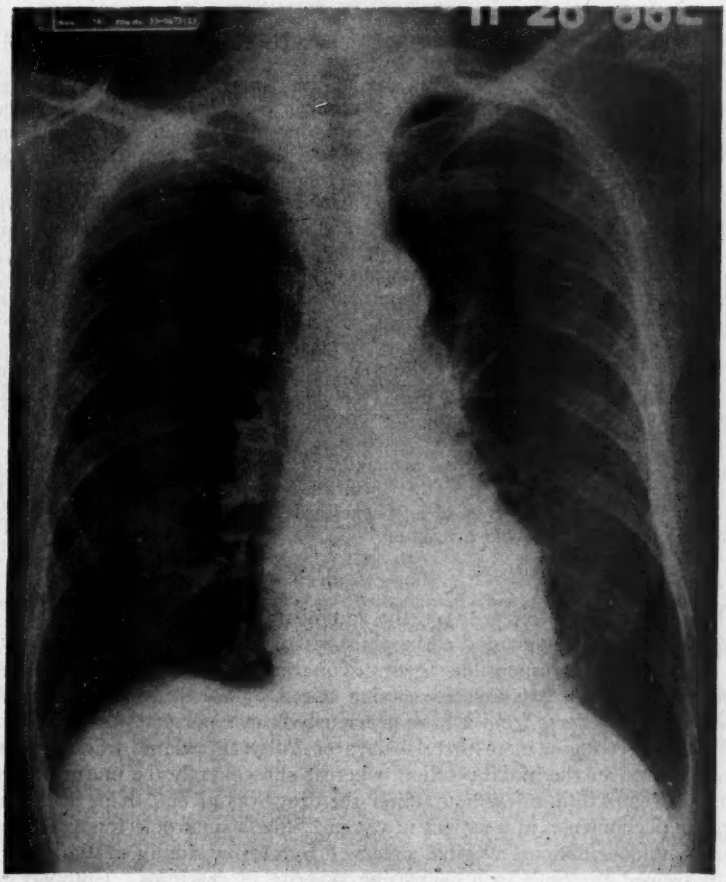

FIG. 3. Roentgenographic appearance of the chest three months after Löffler's syndrome. Lung fields are clear.

penicillin for his urinary tract infection, para-aminobenzoic acid and occasional single doses of acetylsalicylic acid (600 mg.) and secobarbital sodium (100 mg.).

There was gradual improvement in symptomatology. On the twenty-seventh hospital day (August 16, 1955), while the patient was receiving Tolseram and procaine penicillin, he complained of malaise and a nonproductive cough. His temperature, which had been normal, rose to 103°F. Physical examination revealed râles

over the left lower lobe, and a chest roentgenogram disclosed irregular, patchy densities in the left lower lobe. The leukocyte count rose to 12,500 per cubic millimeter, with 15% eosinophils. Fever of 102° F. to 103° F. continued, and serial roentgenograms revealed a spread of the pneumonic process to both upper lobes (figure 2). Eosinophilia persisted, reaching a peak of 24%. Other laboratory studies, including examinations of the stools for ova and parasites, blood cultures, febrile agglutinins, "L.E." cell preparations, sputum cultures for bacteria and fungi, and sputum smears for tuberculosis, were negative. Skin tests for tuberculosis, histoplasmosis and coccidioidomycosis were negative. There was no improvement with tetracycline and Nystatin therapy.

On August 28, 1955, the twelfth day of the patient's febrile illness, Tolseram was discontinued. There was an immediate fall in temperature and improvement in the patient's general condition. There was a slow decrease in eosinophilia and a gradual clearing of the chest roentgenogram. At the time of the patient's discharge on October 19, 1955, he was afebrile and asymptomatic. The leukocyte count was 7,200 per cubic millimeter, with 7% eosinophils. The chest roentgenogram was within normal limits.

The patient was re-admitted on November 17, 1955, for further studies. Following the administration of 2 gm. of mephenesin carbamate, there was an immediate rise in temperature to 101° F., accompanied by cough and malaise. In 72 hours the leukocyte count, which had been normal, rose to 10,300 per cubic millimeter, with 18% eosinophils. Chest roentgenograms revealed a small area of infiltration, which cleared rapidly (figure 3). On two subsequent occasions, 2 and 4 gm. of Tolseram produced a prompt but transient febrile reaction, associated with mild constitutional symptoms and eosinophilia. The impression was that each successive course of Tolseram was attended by a less severe reaction.

The administration of procaine penicillin, para-aminobenzoic acid, acetylsalicylic acid and secobarbital sodium, the other medications the patient had received, did not produce a reaction. A course of mephenesin lacking the carbamate conjugation (Tolserol) also failed to evoke a reaction.

Discussion

The close relationship between the administration of Tolseram and the episodes of fever, pneumonia and eosinophilia seems to warrant the conclusion that this drug was the responsible agent. Tolseram is a carbamic acid ester of mephenesin which exerts muscle-relaxing effects by a central depressant action. No serious side-effects from it have previously been reported.[14]

It is interesting to note that 17 days of Tolseram administration were required to produce the initial reaction, whereas subsequently the untoward effects were apparent within a few hours after the drug was given. Klinghoffer noted a similar phenomenon in a patient in whom Löffler's syndrome was produced by a sulfonamide-containing vaginal cream.[9] Successive administrations of Tolseram seemed to result in a decreasing severity of reactions. Cuthbert noted this in a patient in whom para-aminosalicylic acid produced a Löffler's syndrome.[13] He eventually desensitized the patient with repeated small doses of the drug, and was able to resume antituberculous therapy using the original doses of para-aminosalicylic acid.

Summary

A case of Löffler's syndrome apparently secondary to the administration of mephenesin carbamate (Tolseram) is reported. The syndrome of fever, pulmonary infiltration and eosinophilia was reproduced by reëxposure to the drug.

Although 17 days of Tolseram administration were required to produce the initial reaction, subsequent episodes occurred within a few hours after small doses of the drug were given.

Successive courses of Tolseram were attended by reactions of decreasing severity, suggesting the possibility of desensitization.

Summario in Interlingua

In le caso typic, syndrome de Löffler es characterisate per transitori infiltrationes pulmonar que es frequentemente migratori, per eosinophilia, e per su curso benigne que non manifesta multe symptomas. Le natura allergic de iste syndrome pare esser definitemente establite, e un extense varietate de agentes es incriminate como allergenos. Infestation helminthic, amebiasis, brucellosis, e coccidioidomycosis ha occurrite in association con syndrome de Löffler. Ha etiam essite reportate casos de syndrome de Löffler occurrente post le uso de Prontosil, de sulfonamidos, de penicillina, e de acido para-aminosalicylic.

Es presentate un caso in que un aspecto clinic de character compatibile con syndrome de Löffler occurreva post le uso de carbamato de mephenesina (Tolseram). Le mesme aspecto clinic se reproduceva subsequentemente a tres occasiones post breve administrationes del droga mentionate. Le patiente esseva un homine de 77 annos de etate. Ille disveloppava febre, infiltrationes pulmonar, e eosinophilia que se resolveva promptemente quando le administration de Tolseram esseva arrestate. Le episodio initial occurreva post un curso therapeutic de 17 dies de Tolseram, sed subsequentemente le symptomas se manifestava intra alicun horas post le administration del droga. Administrationes successive de Tolseram pareva resultar in un diminution del severitate del reaction. Isto suggere le possibilitate de un processo de dissensibilisation. Le patiente monstrava nulle reaction a mephenesina sin conjugation carbamatic (Tolserol). Reactiones a Tolseram es infrequente. Secundo nostre informationes, nulle simile caso ha essite reportate.

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ANURIA FOLLOWING RETROGRADE PYELOGRAPHY *

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SINCE 1897, retrograde pyelography has been used in studying diseases of the genitourinary tract. This is the method of choice for studying patients who are sensitive to contrast material given intravenously. We have studied a patient in whom unique sensitivity resulted from contrast media administered in retrograde fashion. Review of the urologic literature has revealed no similar case.

CASE REPORT

A 35 year old man was referred on April 23, 1955, to the urologic service of the Graduate Hospital of the University of Pennsylvania for study because he had been passing red blood cells in his urine following back injury. He was admitted to the hospital with the chief complaint of low back pain and numbness of the right thigh. Neither the patient nor his family gave a history of allergy. The physical examination revealed a well developed and well nourished, healthy looking man who appeared to be his stated age. Physical findings were normal. His blood pressure was 110/80 mm. of Hg; pulse, 80; respiration, 20. No palpable masses, pain or tenderness were found in the abdomen. Examination of his back revealed spasm and tenderness of the right flank muscles, worsened on bending. Percussion of the spine produced pain which was localized over the third and fourth lumbar vertebrae. The prostate gland by palpation was normal in size and consistency. The scrotum and its contents were normal in all respects.

Laboratory Examinations:

Blood: Erythrocytes, 4,730,000/cu. mm. Hemoglobin, 13.8 gm.%. Leukocytes, 12,700/cu. mm. Neutrophils, 70%. Lymphocytes, 21%. Monocytes, 3%. Eosinophils, 6%.

Fasting Blood Sugar: 77 mg.%.

Blood Urea Nitrogen: 13 mg.%.

Blood Wassermann: Nonreactive.

Urinalysis: Color, amber, clear. Sediment, none. Reaction, acid. Albumin, absent. Glucose, absent. Casts, occasional, hyaline. Leukocytes, 5 to 20/hpf. Erythrocytes, 50 to 100/hpf. Amorphous material, slight.

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On April 25 cystoscopic examination revealed a normal bladder. Both ureteral orifices were normal in size, position and configuration. Number 6 F x-ray ureteral catheters were passed 25 cm. on each side. Urine from both kidneys, after culture, showed no growth in 48 hours. Two cubic centimeters of the intended 8 c.c. of contrast medium (Skiodan 15%) were injected into both sides simultaneously. The patient immediately complained of severe back pain in both costovertebral angle regions. He was so agitated he attempted to jump from the table. Although an insufficient quantity of contrast medium had been used, x-ray pictures taken immediately showed normal calyceal configuration bilaterally. The patient, writhing with a colicky but sustained pain, was returned to his room and treated with meperidine hydrochloride, 100 mg., and secobarbital, 90 mg., for analgesia and sedation. Through the night it became apparent that no urine was being passed. In addition, the medication provided no relief from the intense pain and anxiety. Pain and tenderness in both flanks persisted throughout the night. The next morning (April 26) the blood pressure rose to 140/78 mm. of Hg, while the blood urea nitrogen rose to 40 mg.%. A modest amount of sedatives and analgesics provided no improvement during the next 48 hours. Complete anuria persisted. This fact was verified by urethral catheterization. Laboratory examinations were as follows: Serum carbon dioxide capacity, 19 mEq./L. Serum chloride, 93 mEq./L. Serum sodium, 141 mEq./L. Serum potassium, 4.9 mEq./L. Serum calcium, 10.1 mg.%. Blood urea nitrogen, 56 mg.%. Serum creatinine, 7.3 mg.%. Serum bilirubin, direct, 0.33 mg.%. Serum bilirubin, total, 0.94 mg.%.

The patient was treated supportively with intravenous administration of 500 c.c. of 10% glucose containing 40 mEq. of sodium lactate in the morning, and 1,000 c.c. of 5% glucose containing 80 mEq. of sodium lactate in the afternoon. The patient continued to complain of pain. A scout film of the abdomen showed an increase in renal shadow outline. Because the patient was agitated and complaining of "intolerable" pain, neither of which could be relieved with modest amounts of narcotics and barbiturates, and because of the complete anuria at 72 hours following the pyelography, it was decided to attempt to pass a catheter into at least one ureter. Under general anesthesia a cystoscopic examination revealed 30 c.c. of urine in the bladder. Both ureteral orifices were inflamed and edematous. A Number 6 F catheter was passed 25 cm. into the right ureter, and a Number 5 F catheter the same distance into the left ureter. Both yielded a rapid drip of urine, indicating pressure due to hydronephrosis. Three hundred cubic centimeters of urine were obtained from the left side and 275 c.c. from the right. Both catheters were fixed in position. On awakening the patient was entirely free of pain. Serum carbon dioxide capacity, 27 mM/L. Serum chloride, 91 mEq./L. Serum sodium, 135 mEq./L. Serum potassium, 3.8 mEq./L. Serum calcium, 9.3 mg.%. Blood urea nitrogen, 48 mg.%. Serum creatinine, 3.2 mg.%.

During this day flow from the left catheter stopped. The previous characteristic left flank pain developed. The attending resident irrigated the catheter with pressure from a syringe and the pain became worse. The irrigation opened the catheter and free flow ensued, with immediate relief of pain. The subsequent course was uneventful. The patient was discharged on the fifth day, at which time the laboratory studies were as follows: Serum carbon dioxide capacity, 30 mM/L. Serum chloride, 95 mEq./L. Serum sodium, 137 mEq./L. Serum potassium, 4.0 mEq./L. Blood urea nitrogen, 32 mg.%. Serum creatinine, 1.5 mg.%.

Discussion

We presume the cause of this unusual episode of anuria following retrograde pyelography was bilateral ureteral obstruction due to acute edema of the

ureters, resulting from a local sensitivity reaction to the contrast material (Skiodan 15%). This was further suggested by a positive intradermal test done on the second day of anuria. The patient was relieved of pain and anuria after ureteral catheterization. The presence of urine in the bladder 72 hours after pyelography suggests that the block had been opening spontaneously. Extrarenal uremia as a cause can be excluded because the patient had good peripheral circulation, normal blood pressure and a normal state of hydration. Diagnoses of acute tubular necrosis and interstitial nephritis due to sensitivity to contrast material through pyelorenal backflow were excluded by clinical, laboratory and x-ray findings. Furthermore, relief of pain followed passage of urine, renewal of pain followed block, and irrigation again relieved the obstruction and pain. This suggests that this syndrome was the result of ureteral edema. This case is considered extremely unusual, as we have been employing Skiodan 15% for retrograde pyelography for 11 years with no previous difficulty.

Summary

An unusual case is reported of anuria following retrograde pyelography due to extensive edema of both ureters, resulting from sensitivity to Skiodan 15% and causing complete bilateral obstruction of both ureters.

Summario in Interlingua

Acute dolores e anuria sequeva le injection ureteral del substantia de contrasto Skiodan in un studio routinari de pyelographia retrograde. Intra 72 horas, azotemia habeva resultate. Le nitrogeno de urea montava ab 13 usque a 56 mg pro cento. Le creatinina montava usque a 7,3 mg pro cento. Sever dolores persisteva. Le patiente esseva tractate supportativemente con fluidos, lactato de natrium, e analgesicos. Esseva supponite que le grande dolor e le crescente azotemia esseva le resultato de un obstruction ureteral causate per un reaction de sensibilitate e per edema. A causa del non-subjugabile dolor e a causa del anuria, un examine cystoscopic esseva effectuate post 72 horas. Isto revelava edema bilateral al circumferentia de ambe orificios ureteral. Le introduction de catheteres ureteral resultava in un alleviamento immediate del dolores e in le effluxo de 300 e 75 cm^3 de urina ab le un e le altere latere. Le catheteres remaneva in position durante 24 horas. Postea illos esseva eliminate. Post 48 horas le creatinina habeva descendite a 1,5 mg pro cento, e le anormalitates chimic e clinic habeva disparite. Iste problema inusual es discutite, e le tractamento es describite in detalio.

GASTRIC VOLVULUS: A CASE REPORT OF ORGANO-AXIAL VOLVULUS WITH RECOVERY *

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Gastric volvulus is generally considered to be a rare condition and is infrequently reported, although it was described by Berti as early as 1866.[1] It

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occurs with sufficient frequency, however, that it should not be overlooked as a possible explanation for acute, intermittent or chronic upper abdominal symptoms, especially with gastric obstruction in the presence of hiatus hernia. The diagnosis may be difficult, and requires both clinical and roentgenologic evidence, but in many cases the findings may be typical and the diagnosis easily made if gastric volvulus is considered. Early diagnosis is essential in those cases presenting as an acute emergency.

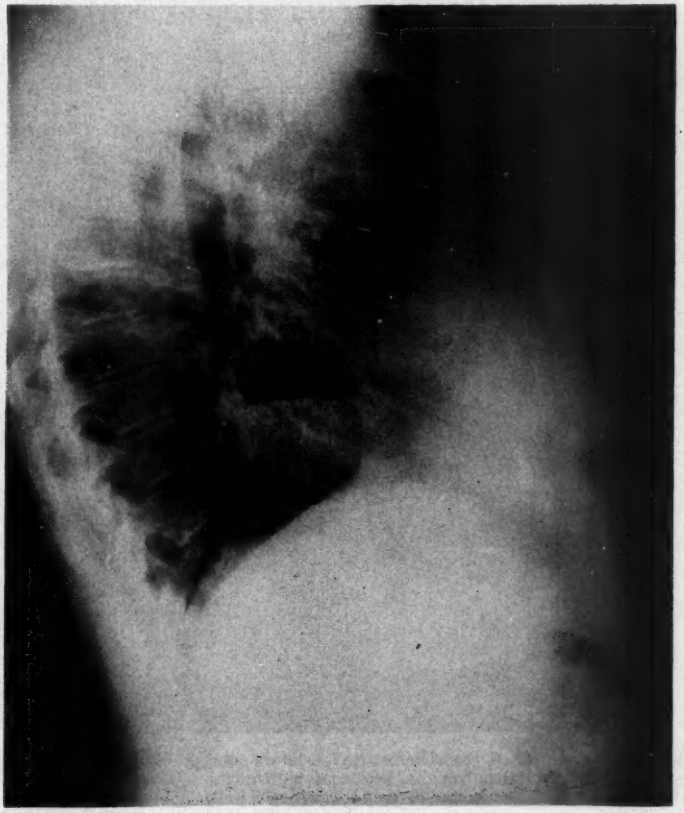

FIG. 1. Left lateral projection of the chest roentgenogram made in 1953. Moderately large hiatus hernia with an air-fluid level is seen.

Volvulus implies a torsion of the organ. The stomach is held firmly by the cardia and, to a lesser extent, by the pylorus. The torsion can occur in two planes: the coronal, in which the stomach twists about its organic axis either anteriorly (more commonly), or posteriorly, and the sagittal, in which there is rotation about the mesenteric axis. In either case the volvulus may be partial, complete or intermittent, with spontaneous reduction.

The literature has recently been reviewed by Gottlieb, Lefferts and Beran-

baum.[2] Seven cases, two of which occurred as postoperative complications, have recently been reported.[3]

Case Report

The patient, a 75 year old widow, had been in her usual state of health until September 11, 1955. While eating her supper she had a choking sensation in the lower substernal region and was unable to swallow any more food. She soon began

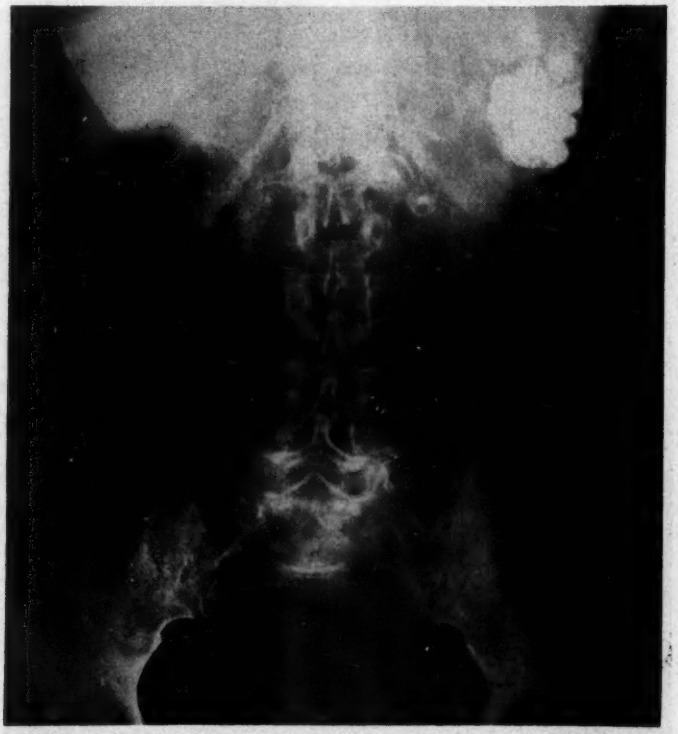

Fig. 2. A scout film of the abdomen in posterior-anterior projection reveals a large cluster of partially dissolved tablets of Telepaque high in the left upper quadrant overlying the approximate area of the fundus of the stomach. A well calcified splenic artery is seen medial to this.

to vomit, and developed a pain in the lower substernal and upper epigastric region. She was uncomfortable during the night, and when first seen the next morning she complained of diffuse, moderately severe pain in the upper abdomen and lower substernal region. She retched frequently, but appeared well hydrated. There was some tenderness in the epigastrium, but the physical findings were otherwise no different than in the past. She was given an injection of Demerol because of the tentative diagnosis of cholelithiasis. She continued to have a pain associated with retching, and was admitted to the hospital the next day. She had a normal bowel movement the day the symptoms began, but none afterwards. She stated that in

the past she had had similar though milder episodes, lasting for from 30 to 90 minutes and usually relieved by vomiting.

In 1953 the patient had been found to have cardiac decompensation due to calcareous aortic stenosis. At that time a roentgenogram of the chest revealed the heart to be within normal limits of size and configuration, and the lungs to be clear. On lateral chest film a large air-fluid level was seen posterior to the heart (figure 1)

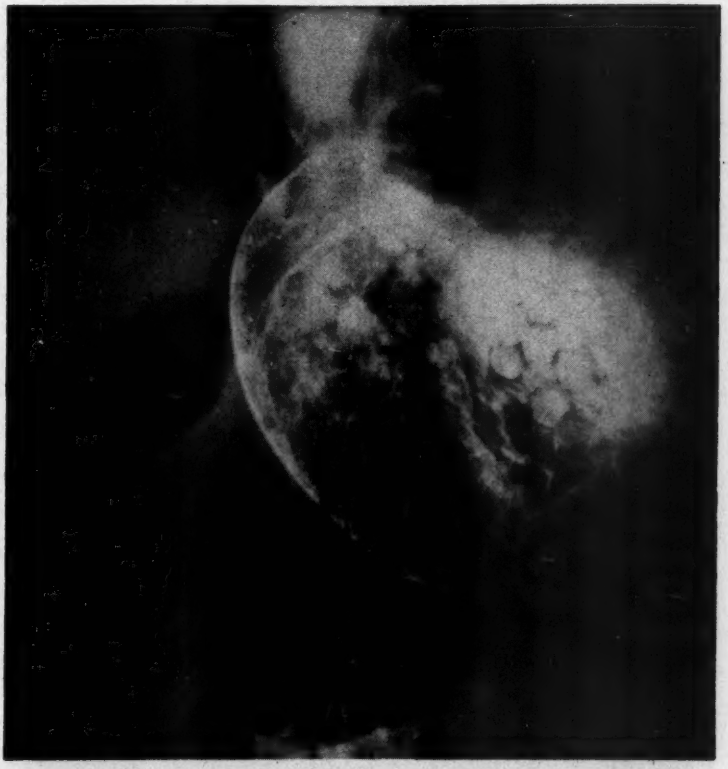

FIG. 3. Posterior-anterior view of the abdomen following a barium meal reveals a mixture of barium, Telepaque and fluids in the stomach. The mesial wall of the stomach was determined fluoroscopically to represent the greater curvature. The identity of the pyloric end of the stomach is lost on this projection. The lesser curvature surface of the stomach is seen near the superior outline of the barium contrast medium.

which was thought to represent a large hiatus hernia. The decompensation was well controlled with digitalis and moderate salt restriction. In December, 1954, following several months' weight loss associated with good appetite and increased fluid intake, a diagnosis of diabetes mellitus was made. The decompensation continued to be well controlled with digitalis. The patient was moderately well regulated on 25 units of NPH insulin daily and 1,800 calories (American Diabetic Association diet). She had memory loss and difficulty in concentrating, changes thought to be due to senility.

On the present admission to the hospital the blood pressure was 140/80 mm. of Hg. The pupils were round, regular and equal, and the fundi revealed only moderate sclerosis of the arterioles, without evidence of any diabetic retinopathy. The tongue was dry. The lungs were clear. The heart appeared slightly enlarged to the left; the rhythm was regular. There was a harsh blowing grade III systolic murmur, loudest over the aortic area, accompanied by a definite thrill. The abdomen was soft, with definite tenderness over the upper abdomen as well as the lower costal

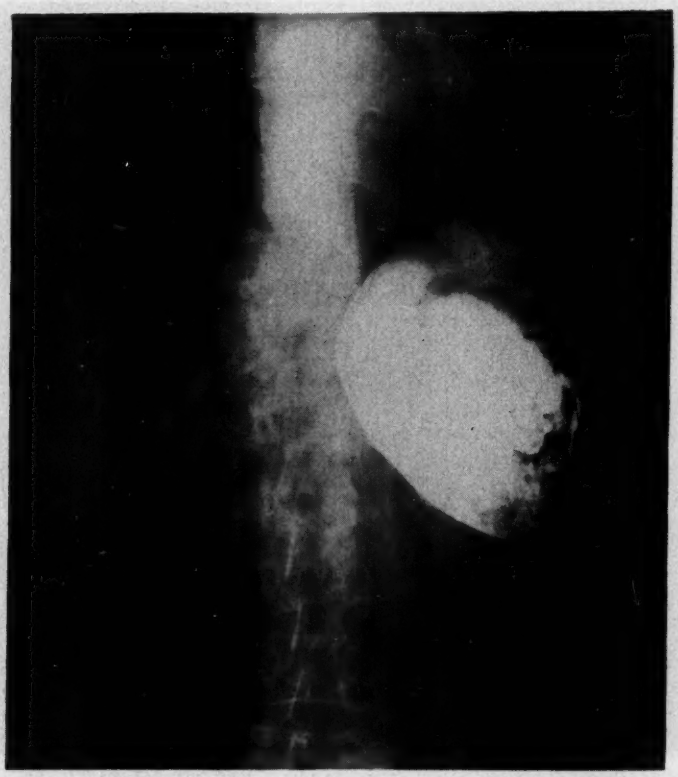

FIG. 4. Anteroposterior projection of the stomach following the barium meal reveals essentially the same configuration of the stomach as is described in figure 3. Reflux of the barium meal into the esophagus is well demonstrated, and there is slightly greater contrast between the superiorly projecting lesser curvature of the stomach and the fluid-containing main body of the stomach.

margin. The patient was unable to localize the pain. Peristaltic sounds appeared normal. On rectal examination, hard fecal masses were felt but no other abnormalities were noted. The rest of the physical examination was not remarkable.

Urinalysis showed a specific gravity 1.020, a slight trace of albumin and 1% glucose. The hemoglobin was 14.5 gm.%; leukocytes, 13,400 per cubic millimeter, with 74% neutrophils, 2% eosinophils, 22% lymphocytes and 2% monocytes. The blood sugar on admission was 279 mg.%. An electrocardiogram showed changes consistent with digitalis effect.

The patient was given digitoxin, Thorazine intramuscularly in an effort to control the vomiting, insulin as necessary, and intravenous fluids. On the day after admission a cholecystogram revealed that tablets of Telepaque were retained in the stomach after 12 hours (figure 2). On the next day an upper gastrointestinal series revealed a dilated stomach with retained fluids. The greater curvature was convex and to the right, and there was a partial invagination of the anterior wall of the stomach. The radiologist concluded that this was an organo-axial volvulus stomach with complete obstruction (figures 3, 4 and 5).

FIG. 5. Left lateral projection of the abdomen following a barium meal demonstrates the lesser curvature surface of the stomach at its distal end to project superiorly. There is considerable invagination of the anterior surface of the stomach, allowing the lesser curvature to assume this position.

Preparation for immediate laparotomy was made. At surgery numerous adhesions to the lower abdominal incision were noted. The stomach was found to be twisted on itself so that the greater curvature now lay in the region of the lesser sac. There was an incarcerated hiatus hernia approximately two to three inches in diameter. A band of gastrocolic omentum lay about the stomach, and it was necessary to untwist the stomach through this band in order to reduce the volvulus. After the hernia was reduced and the band of omentum incised, ischemia was noted in the antrum of the stomach, but the color returned to this area soon. No other

abnormalities were noted. Figure-of-eight sutures were placed in the hiatal hernia ring, reducing its opening until it barely met two fingers, and the junction of the esophagus and the stomach was sutured with two catgut sutures to the repaired portion of the diaphragm.

Following operation the patient had an uneventful recovery. The diabetes was easily controlled. Her symptoms were relieved, and there have been no other episodes of abdominal pain and vomiting.

Discussion

Gastric volvulus has been classified in various ways, but most authors use the system first proposed by von Haberer [4] and later modified by Singleton.[5]

I. Type:
   (a) Organo-axial: Rotation of the stomach around the long axis of the stomach, i.e., around the coronal plane.
      1. Supracolic
      2. Infracolic
   (b) Mesentero-axial: Rotation of the stomach from right to left or left to right about the long axis of the gastrohepatic omentum, i.e., the sagittal plane.

II. Extent:
   (a) Total: Cases in which the whole stomach except the diaphragmatic attachment rotates.
   (b) Partial: Instances in which the rotation is limited to a segment of stomach, usually the pyloric end.

III. Direction:
   (a) Anterior: Cases in which the rotating part passes forward.
   (b) Posterior: Cases in which the rotating part passes backward.

IV. Etiology:
   (a) Secondary to disease in the stomach or adjoining organs.
   (b) Idiopathic.

V. Severity:
   (a) Acute: Presenting a picture of an acute abdomen.
   (b) Chronic: Causing constant or recurrent milder symptoms, or symptomless.

The etiology is usually important. Most of the recorded cases were secondary to other conditions in the abdomen. Incarceration of a part of the stomach in a hiatus hernia,[6] as in this case, is the most frequent predisposing cause. Other conditions which have been reported as causing gastric volvulus are tumors, peptic ulcers, recent surgery,[3] trauma, marked rapid weight loss, hour-glass stomach,[6] eventration of the diaphragm, adhesions, colonic diverticulitis, and pancreatic malignancy.[2] In some of the cases there was no discernible cause.

In both types of volvulus there must be an abnormality, either congenital or acquired, of the peritoneal and mesenteric attachments of the stomach for the abnormal rotation to occur. In mesentero-axial volvulus a certain atony or lengthening of the peritoneal fixations, and the gastrosplenic, gastrophrenic, hepatogastric and gastroduodenal ligaments, with more or less ptosis of the stomach, has to be present. In organo-axial volvulus there is usually some abnormality, either congenital or acquired, of the gastrohepatic or gastrocolic ligament, or failure of fusion of the omentum to the transverse colon, so that the fundus of the stomach can rotate cephalad. Diaphragmatic hernia as well as

eventration of the diaphragm is undoubtedly a predisposing factor in the lengthening of the mesenteries, and explains the relatively frequent occurrence of volvulus in diaphragmatic hernia. Often there is an associated abnormally long gastrohepatic or gastrocolic ligament or a defect in these ligaments, probably of congenital origin.[2]

Distention of the colon has been suggested as a cause of volvulus and mentioned as a possible cause of some of the symptoms.[8]

The symptoms are extremely variable, and may range from none to a severe abdominal catastrophe. In a typical acute case with complete volvulus, there is sudden epigastric pain, followed by vomiting, which soon turns into an unproductive retching. Shock may ensue and abdominal distention occur. The triad of circumscribed epigastric pain, strong efforts to vomit without results, and inability to pass a stomach tube is said to be diagnostic.[3] In many of the reported cases there were episodes of milder but similar symptoms that were suddenly relieved by vomiting. Apparently in the case reported here there had been previous mild attacks. In chronic incomplete volvulus the symptoms may be vague and consist of indigestion, fullness and slight pain in the epigastrium or in the lower chest.

The differential diagnosis in complete volvulus should include other abdominal emergencies, such as cholelithiasis with colic, ruptured peptic ulcer, or ruptured viscus from any cause, acute pancreatitis, high intestinal obstruction, and mesenteric thrombosis and embolism. Chronic incomplete gastric volvulus may be confused with peptic ulcer, gastritis, functional gastrointestinal disorder or gall-bladder disease, splenic flexure syndrome, hiatus hernia and even coronary artery disease. The intermittent acute attacks may simulate gall-stone colic or incarcerated diaphragmatic hernia.

The diagnosis is best made roentgenographically by an upper gastrointestinal series. In an organo-axial volvulus there may be a double fluid level, produced by gas above the gastric fluid. The antrum is elevated to the level of the fundus,[7] and the greater curvature may lie above the lesser curvature. Narrowing, or an hour-glass appearance, of the body of the stomach, with demonstration of a definite spiral appearance of the gastric mucosa, may be present.

The esophagogastric junction may be low. The colon may be abnormally high, and it has been suggested that a barium enema examination be performed to rule out a lesion of the colon which would push the stomach cephalad.[5] A simple cascade stomach may at times offer difficulty in differential diagnosis in this type of volvulus.[2]

In a mesentero-axial volvulus the stomach is divided into two loculi; the first fills promptly and the second slowly, or not at all if the obstruction is complete. The rugal folds are disturbed and show a screw arrangement at the point of narrowing.[7]

The treatment in the acute, completely obstructed gastric volvulus is of course surgical. At operation the volvulus can be manually reduced and at the same time any secondary causes, such as diaphragmatic hernia, can be repaired. Fixation of the stomach, as by posterior gastrojejunostomy, has been recommended.[8] Others have suggested partial gastrectomy and anterior gastropexy to prevent recurrence.

Subacute or chronic cases may respond to more conservative measures, but it should be remembered that if the torsion is of 180° or more the blood

supply to the stomach is in jeopardy. Also, most of these cases will have recurrences and surgery will become necessary. In chronic incomplete cases, antispasmodics and a bland diet may afford some relief.

Summary

A case is reported of acute organo-axial gastric volvulus in a 75 year old woman with coexisting diabetes mellitus, aortic stenosis and hiatus hernia. She had previously had mild attacks. At operation the cardia of the stomach was incarcerated in the hiatus hernia. The greater curvature of the stomach had apparently passed cephalad through a defect in the gastrocolic ligament.

Gastric volvulus is produced by a rotation of the stomach about its organic axis in the coronal plane or about its mesenteric axis in the sagittal plane. The volvulus may be posterior or anterior, partial or complete. There is some elongation or other abnormality of the mesenteric attachments of the stomach and usually an associated condition, most often a diaphragmatic hernia, which predisposes to the volvulus.

The symptoms vary with the degree of obstruction. In the complete acute volvulus there are epigastric pain, vomiting followed by unproductive retching, inability to pass a stomach tube, abdominal distention and shock. Milder episodes may occur and resolve spontaneously. Chronic incomplete volvulus is associated with such nonspecific symptoms as belching, fullness, and discomfort in the epigastrium or lower chest.

The diagnosis is best made by the characteristic findings on the roentgenograms in conjunction with the clinical picture.

The treatment is usually surgical. An occasional case can be relieved by conservative measures.

Summario in Interlingua

Es reportate un caso de volvulo gastric organo-axial occurrente in un femina de racia blanc de 75 annos de etate in qui diabete mellite e stenosis aortic esseva coexistente. Previemente le presentia de un hernia hiatal habeva essite diagnosticate super le base del constatation de un nivello de aere e fluido in retro del corde in un roentgenogramma thoracic lateral. Le patiente esseva admittite al hospital 36 horas post le declaration de suffocation, vomito, e sever dolores supero-abdominal e infero-thoracic. Post le ingestion de un portion de barium, vistas fluoroscopic e roentgenologic revelava un dilatate stomacho con retenite fluidos. Le curvatura major esseva convexe e dextrorse. Le pariete anterior del stomacho esseva partialmente invaginate, lo que indicava un volvulo organo-axial. Al laparotomia un banda de omento gastrocolic jaceva circa le stomacho. Le patiente se restabliva ab le operation.

Volvulo gastric es producite per un rotation del stomacho circa su axe organic in le plano coronal o circa su axe mesenteric in le plano sagittal. Le volvulo pote esser anterior o posterior, partial o complete. Es presente un certe elongation o alicun altere anormalitate del attachamento mesenteric del stomacho e usualmente etiam un condition associate—le plus frequentemente un hernia diaphragmatic—que predispone al formation del volvulo.

Le symptomas es extrememente variabile e depende del grado de obstruction in le caso individual. Illos pote mancar completemente o amontar a un grave catastrophe abdominal. In complete volvulo acute il ha dolores epigastric, vomito sequite per vomiturition non-productive, impossibilitate de introducer un tubo gastric, distension

abdominal, e choc. Episodios minus grave pote occurrer e resolver se spontaneemente. Chronic volvulo incomplete es associate con symptomas non-specific, incluse eructation, un sensation de repletion, e disconforto in le epigastrio e le thorace inferior.

Le diagnose se face le melio super le base del constatationes characteristic in roentgenogrammas a barium, in conjunction con le aspecto clinic. Le tractamento es usualmente chirurgic. Casos sporadic pote esser alleviate per mesuras conservative.

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ESSENTIAL THROMBOCYTHEMIA *

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Considerable emphasis has been placed recently in the medical literature upon blood platelets and their functions. Much of the work centers around the multiple ways by which platelets influence the blood clotting mechanism. The prevailing evidence is that the first phase of coagulation is the one in which the platelets play their major role,[1] although the additional functions of promoting capillary constriction and clot retraction must be included. A great deal more progress has been achieved in the study of thrombocytopenia than in its counterpart, thrombocythemia. This is undoubtedly due to the fact that a relatively small number of cases of thrombocythemia have been reported.

Thrombocythemia is to be differentiated from thrombocytosis, the former implying a proliferation of unknown etiology and the latter an increase secondary to a known cause.[2] This is analogous to the differentiation of leukemia from leukocytosis.

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It is now well established that thrombocythemia may or may not be connected with a hemorrhagic tendency.[3] This tendency, as well as vascular thromboses, has not been adequately explained, nor is there an explanation for the commonly encountered splenomegaly. Frequent findings in this disease are leukocytosis with immature forms in the peripheral blood, and an increase in the red blood cell count.

This paper presents a patient with repeated episodes of bleeding and certain interesting clinical features not previously reported.

Case Report

A 23 year old white male was first admitted to the Medical Service of McGuire Veterans Hospital January 9, 1952, complaining of bleeding gums. The patient had been in relatively good health until 1943, at which time he fell from a horse, striking his left flank on a log. Within 72 hours he noted a mass in the left upper abdominal quadrant and consulted a local physician, who diagnosed his condition as a damaged muscle. No further investigation or therapy was undertaken. During the following three years he noted a gradually increasing dull pain and swelling in the left upper abdominal quadrant. He was inducted into the military service on February 25, 1946, and was hospitalized 10 days later because of pain of 12 hours' duration in the left upper abdominal quadrant. Pertinent physical findings included marked left upper abdominal quadrant tenderness and a palpable mass filling that entire area. Temperature was 100.2° F. Blood count revealed 17,750 white blood cells, with an increase in polymorphonuclear cells and a shift to the band stage.

A splenectomy was performed four days later. The pathologic description was as follows: *Gross Description:* "Specimen consists of a spleen weighing 2,125 grams, measuring $24 \times 17 \times 10$ cm. The external surface is red-purple but bears wide areas of dull gray discoloration. Over part of the external surface there are discrete and confluent gray nodules measuring .3 cm. in greatest diameter. The external surface is roughened by fibrous tissue tags. Consistency is firm. The splenic notch and hilar notch are rather deep. The cut section is beefy red to gray-red. Trabeculae are visible. At one pole in the cut surface, the tissue is decidedly gray with areas of gray-white discoloration measuring up to 2 cm. in greatest diameter. In places, the capsule is toughened and thickened and measures 3.3 cm. in thickness." *Microscopic:* "In numerous preparations stained with hematoxylin and eosin, the capsule shows uniform thickening. The underlying splenic tissue is unique in its paucity of usually seen splenic components. Trabeculae are scant; Malpighian follicles are sparse and the splenic pulp is only here and there preserved. In the main, the splenic tissue has been replaced by blood and blood products. Gold brown pigment occupies the sinusoids; some small vessels show thrombotic changes. Where blood is absent the splenic pulp is occupied by fibrous tissue. Fibroblasts are numerous. There is an infarct composed of a homogeneous mass of pale staining relatively acellular fibrous tissue with ghosts of splenic tissue within. Abnormal cells are not seen." It was the examiner's impression that this was a hemorrhagic infarct of the spleen.

Following an uneventful postoperative period the patient was discharged on April 24, 1946, only to be re-admitted three days later with complaints of dull, aching left flank pain. There was slight tenderness over the lower part of the abdominal incision. He was discharged after a 10 day period of observation.

The patient was relatively asymptomatic for six months. He then developed typical signs and symptoms of acute appendicitis, and an acutely inflamed appendix was removed. The white blood cell count during this episode was 47,200. He developed an incisional hematoma, which was evacuated and subsequently healed.

He was hospitalized three times during the next nine months for symptoms of intestinal obstruction presumably due to adhesions. The symptoms subsided each time without surgical intervention. The white blood counts during these admissions showed a leukocytosis up to 22,000, eosinophilia up to 34%, and an increase in the number of platelets (no count given).

On October 5, 1947, the patient developed chills, fever (104.2° F.), frontal headache, marked photophobia, vomiting, and cyanosis of the lips and nail-beds. Pulse rate was 144. The white blood cell count was 18,250, predominantly polymorphonuclears, with a marked increase in band forms and 11% eosinophils. In 24 hours

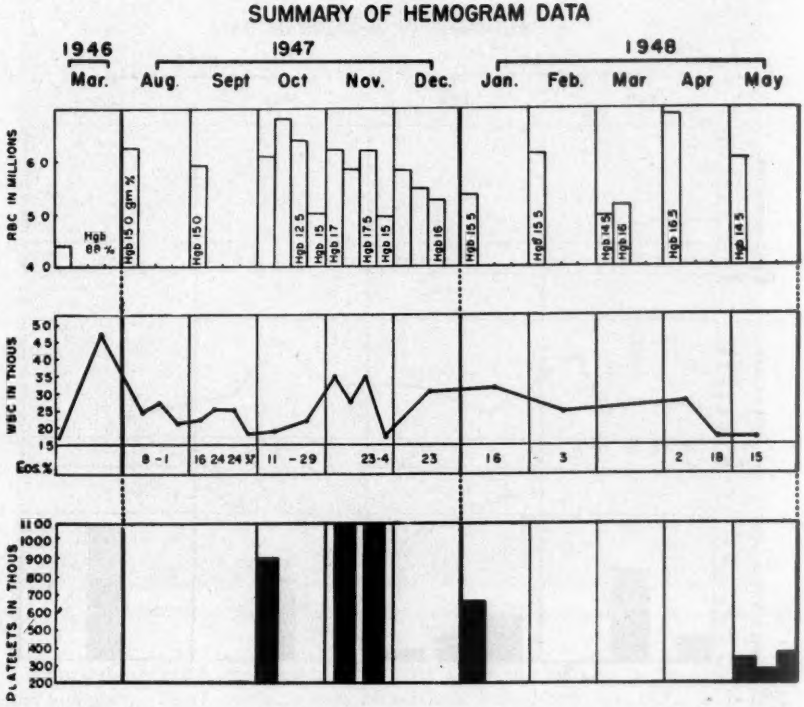

CHART 1.

a slight improvement was noted. Serum proteins and albumin-globulin ratios were normal. Blood culture yielded no growth. Urine examination revealed 150 mg.% of albumin. Three days later he became icteric, and a tentative diagnosis of homologous serum jaundice was made. Leukocytosis and polycythemia were again noted. Two days later the icteric index was 56 units. A sternal marrow aspiration revealed myeloid hyperplasia with eosinophilia. The erythroid elements were normal despite the increased peripheral red blood cell count (6.79 million). Megakaryocytes were abundant.

During the following week the bleeding and clotting times were normal, but the clot retraction was poor and the platelet count was 900,000. The red blood cell fragility was decreased.

By November 4, 1947, the jaundice subsided. Blood counts continued to show elevations of both the red and white series, with clumping of the red cells in Hayem's solution, necessitating the use of saline for red blood cell count. Platelet count revealed 1.1 million platelets per cubic millimeter.

In December, 1947, following a tooth extraction, it was noted that bleeding was difficult to control for 24 hours.

During the next six months the patient's course was relatively uneventful, aside from a persistent increase in both red and white blood cells in the peripheral blood and mild paroxysmal headaches. Platelet counts were within normal range. In May, 1948, the clot retraction was poor and the prothrombin concentration was 29%.

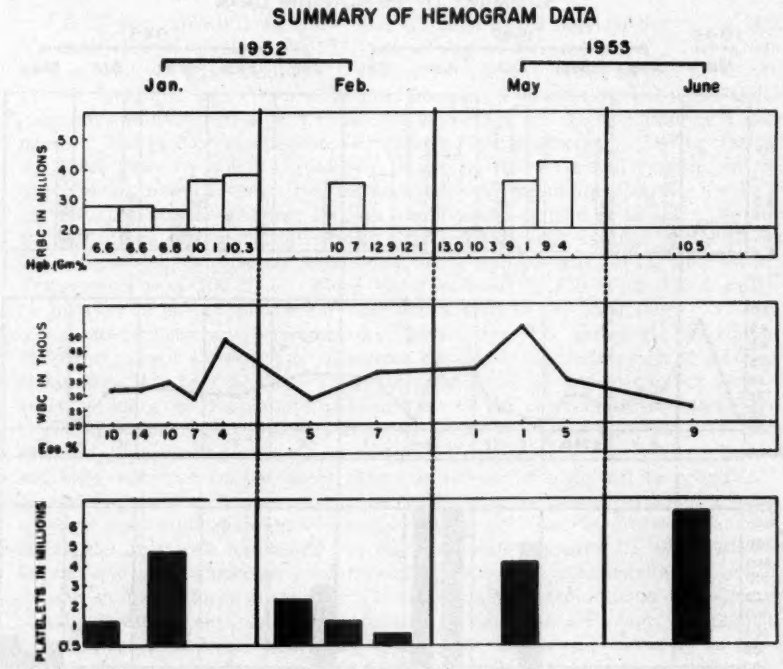

CHART 2.

On July 7, 1948, he was separated from the military service with the diagnosis of blood dyscrasia, type undetermined. The results of the hematologic examinations performed while the patient was in military service are summarized in chart 1.

At the time of the patient's first admission to the McGuire Veterans Hospital, on January 9, 1952, his chief complaint was bleeding from the mouth. He stated that since separation from the service in 1948, he had had periodic similar episodes, occurring at two to three week intervals. Two weeks prior to admission he had noticed increasing gingival bleeding, and following a tooth extraction the bleeding lasted for seven days.

Subsequent to discharge from the service in 1948, the patient had felt gradually increasing weakness, lethargy and fatigue, with periodic episodes of vertigo and syncope, lasting only a few seconds and sometimes accompanied by blurring of vision.

He also complained of nocturia, low back pain and occasional slight ankle edema. He had been working during this time as a bus driver.

Physical examination revealed a pale, fatigued 23 year old white male. Blood pressure was 128/82 mm. of Hg. Pulse rate was 84. Temperature was 98.6° F. The second molar tooth of the right maxilla was absent and there was a fresh clot in the socket. The oral mucous membranes and pharynx were pale. There were well healed abdominal scars at the sites of former splenectomy and appendectomy. Slight pain was elicited by percussion of the midlumbar area. The skin was pale, without evidence of petechiae or ecchymosis.

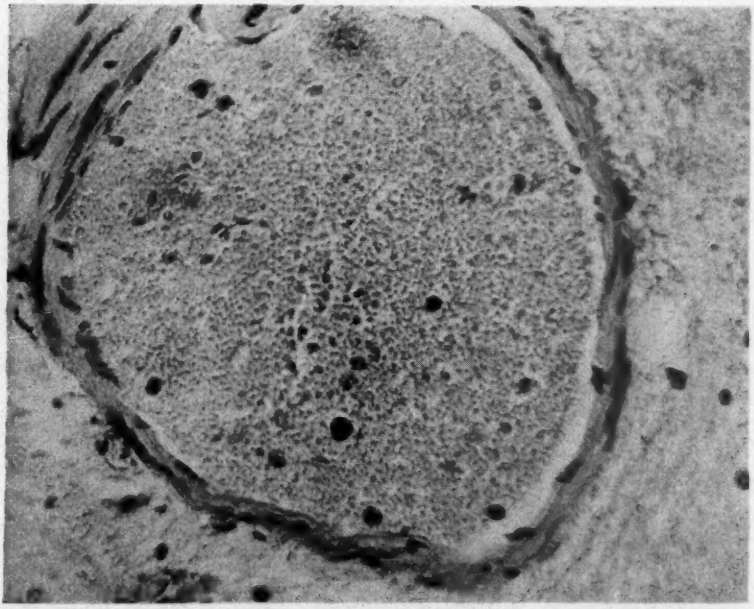

FIG. 1. A cerebral blood vessel filled with platelets. Note scattered leukocytes and erythrocytes (× 440).

Urinalysis revealed albuminuria with casts and some red and white blood cells in the sediment. There was a marked anemia and leukocytosis (31,100), with 10% eosinophils. There were 1,100,000 platelets per cubic millimeter. Coagulation and prothrombin times were normal. Rumpel-Leede's test was negative. Sternal marrow examination was reported as normal except for a slight eosinophilia.

The patient's bleeding time gradually rose to two hours. He was given 20 mg. of protamine sulfate intravenously because of a positive protamine heparin titration (Le Roy and Halpern method). The following day the platelets rose to 4.63 million per cubic millimeter. Bleeding time decreased to 8 minutes. The patient also received four pints of whole blood, with a subsequent rise in hemoglobin. He was discharged after five weeks with a diagnosis of essential thrombocythemia.

The patient was not seen again until May, 1953, when he was admitted because of protracted bleeding following multiple tooth extractions. Blood pressure was 148/108 mm. of Hg. The most remarkable hematologic findings were a bleeding time of one hour and 50 minutes, a marked increase in platelets, and a white blood

cell count of 37,500. He was treated with thrombin and gelfoam packs, which stopped the bleeding. His hemoglobin level rose spontaneously, and he was discharged after 11 days.

His final admission was on June 15, 1953, after a relatively symptom-free interval. Laboratory studies revealed a leukocytosis of 23,100, with 9% eosinophils and 6.57 million platelets per cubic millimeter, but a normal bleeding time. Shortly thereafter the patient was discharged. The hematologic studies performed in the course of four admissions to the McGuire Veterans Administration Hospital are summarized in chart 2. After an interval of about two months the patient was found dead in a local hotel. An autopsy was performed by the Office of the Chief Medical

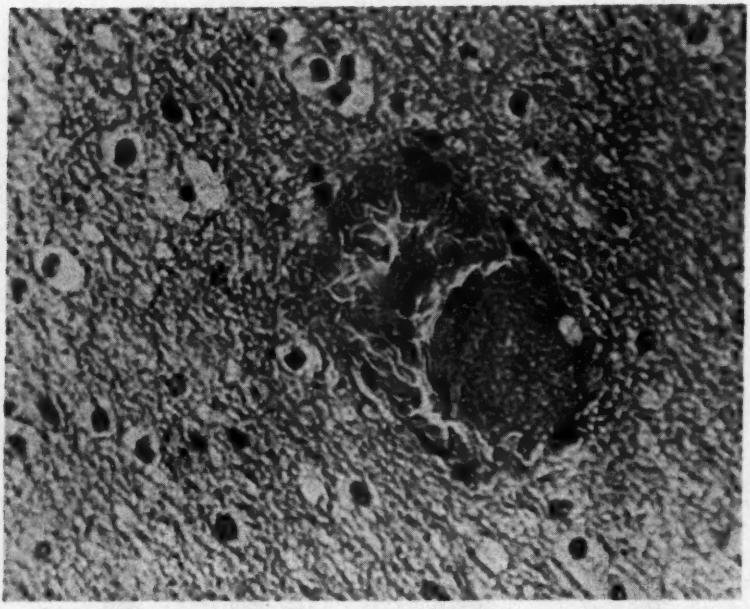

FIG. 2. Cerebral blood vessel containing a conglutinated platelet thrombus (× 440).

Examiner nine hours after death. There were two well healed surgical incisions over the abdomen. No other external findings of note were present. On internal examination the body cavities were unremarkable except for adhesions around the cecum. All of the viscera were congested but otherwise showed no significant gross changes, except for the kidneys. Each kidney weighed 200 gm., had an adherent capsule, and a finely granular surface. The cortical-medullary differentiation was poor, and there were small, irregular, yellowish gray areas scattered throughout the cut surface. The pelves, ureters and bladder appeared normal. The spleen was absent. The brain was congested and edematous, weighing 1,500 gm. The basilar vessels were filled with a thick, creamy fluid.

Microscopic examination of the brain revealed striking intravascular changes. Many arteries and veins were filled with masses of pale eosinophilic platelets. The individual platelets were distinctly outlined. A few erythrocytes and leuko-

cytes were mixed in the stream of platelets (figure 1). This was not a uniform finding, since some vessels contained merely erythrocytes and leukocytes. This indicated that the platelets formed a sufficiently large portion of the blood current to be conspicuously visible after blood-settling in the body took place. In addition, the brain showed several small vessels similarly distended and packed with conglutinated platelet masses. The individual outlines of the platelets were obliterated (figure 2). It was felt that these changes represented early platelet thrombosis. While no cerebral infarcts were found, there were small areas of tissue dissolution and focal areas of early glial cell proliferation with neuronal satellitosis. Individual

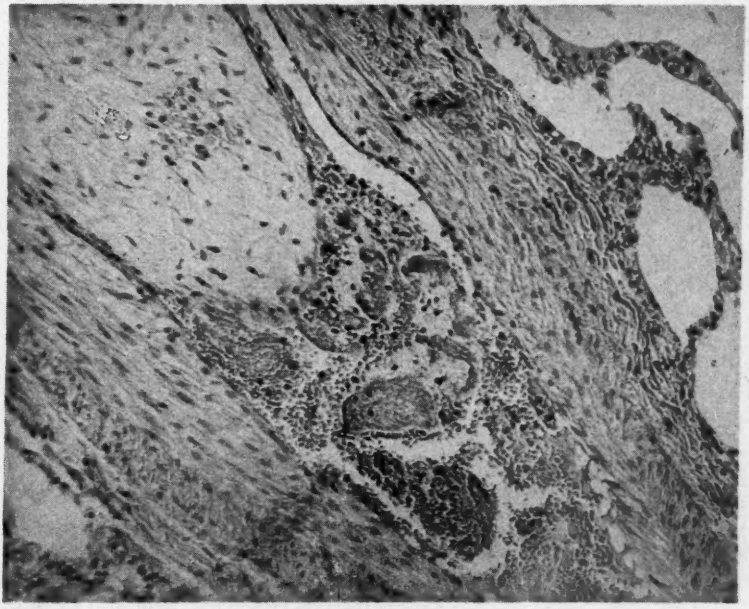

FIG. 3. A partially organized thrombus in a pulmonary artery (× 100).

neurons were undergoing degeneration, some being shrunken and pyknotic, others swollen and anuclear. Fresh and organized thrombi were also found in the smaller branches of the pulmonary artery (figure 3). No infarcts were found in the lungs.

The bone marrow was very cellular, with a decreased amount of fat. Both the erythroid and myeloid series shared in the hyperplasia, and each was maturing in normal fashion. The megakaryocytes were conspicuously increased (figure 4). They had normal nuclei and granular cytoplasm. Other findings of note were slight scarring of the myocardium and a moderately severe degree of bilateral chronic pyelonephritis. Pathologic diagnoses were: (1) essential thrombocythemia; (2) platelet thrombi in cerebral vessels; (3) focal degenerative changes of the brain; (4) thrombi of pulmonary arteries; (5) megakaryocytic hyperplasia of the bone marrow; (6) chronic pyelonephritis; (7) surgical absence of the spleen.

The staff of the Armed Forces Institute of Pathology concurred in the interpretation of this case as one of hemorrhagic thrombocythemia which, from the available evidence, was thought to be unassociated with any other form of myeloproliferative disorder. This observation was supported by the absence of myeloid metaplasia in the available sections of liver and lymph nodes. The diffuse hyperplasia of the granulocytic and erythroid elements in the bone marrow was considered to be nonleukemic. The platelet thrombi in the cerebral vessels were thought to be related to the patient's death. However, no conclusive evi-

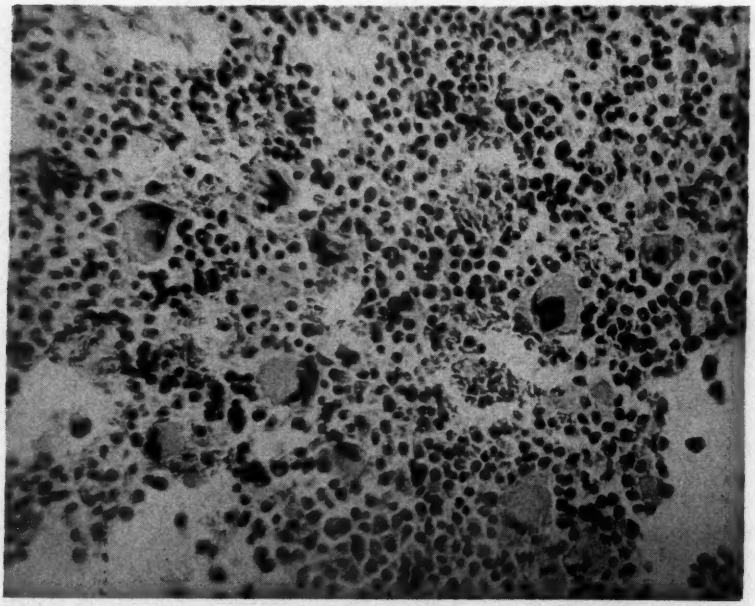

FIG. 4. A section of highly cellular bone marrow with many megakaryocytes (× 440).

dence of ischemic necrosis was found in any of the available tissues. The results of toxicologic examinations performed on the postmortem material were negative.

REVIEW OF LITERATURE

Various authors have described the phenomenon of an abnormally high platelet count under such different titles as essential thrombophilia,[4, 5, 6] hyperthrombocytic myelosis,[3] essential thrombocythemia [2, 4, 7, 8] and thrombocythemia hemorrhagica.[9] Spangberg and Zettergren [2] discussed the problem of whether the entity should be referred to as thrombocythemia or thrombocytosis. The latter would represent a hematologic change secondary to another condition. This is often seen in polycythemia vera, myelogenous leukemia, tuberculosis, some

acute infections, following splenectomy, and occasionally in the course of some neoplastic diseases. Reid [10] considers thrombocytosis a temporary disorder and thrombocythemia permanent. The exact position of thrombocythemia in the over-all scheme of hematologic disorders is another point of contention. Spangberg and Zettergren [2] place it within the group of myeloproliferative disorders, which include also polycythemia vera and myelogenous leukemia. The presence of megakaryocytic hyperplasia in the bone marrow and splenomegaly support this viewpoint. Myeloid leukemia and erythremia usually manifest themselves by an increase in only one of the cellular blood elements, whereas thrombocythemia is more often associated with an increased erythrocyte and leukocyte count. Hickling [11] reported nine cases of thrombocythemia with a tendency toward polycythemia, leuko-erythroblastic anemia, myelogenous leukemia or myelosclerosis. Polycythemia may be masked by blood loss [2] in the hemorrhagic type of thrombocythemia.

Fanger et al.[7] reviewed 28 cases of thrombocythemia, but considered only two of them as idiopathic.

Venous thromboses associated with an increase in platelets, red and white blood cells as well as hepatomegaly and splenomegaly were reported by Epstein and Goedel,[12] Reid [10] and Holst.[13] Arterial occlusions in the heart, kidneys and brain, without significant degenerative or inflammatory vascular lesions, were recorded in five patients by Nygaard and Brown.[6] Megakaryocytic hyperplasia of the bone marrow was a constant feature in their series.

The existence of a hemorrhagic tendency in the presence of abundant platelets is a paradoxic finding. Moolten, Vroman and Vroman [15] postulate that there may be qualitative variations in the platelets. They have demonstrated that in some instances there is an increased adhesiveness leading to platelet thrombi, with subsequent hemorrhage. A sudden increase in the platelet count was interpreted as a danger signal, just preceding hemorrhage. Marmont and Palmieri [14] found that the increase in the number of platelets increased the resistance of the blood to the action of heparin.

The cardinal features of the disease are hemorrhagic diathesis, tendency to thromboses, splenomegaly, megakaryocytic hyperplasia of the bone marrow, leukocytosis, thrombocytosis and erythrocytosis.[2] The latter may at times be masked by blood loss. All these findings were present in our case.

It is difficult to believe that the original trauma was the sole cause of the splenomegaly; more likely, it merely served to focus the patient's subsequent attention to this area. The presence of fresh thrombi in the brain and organized thrombi in the lung at autopsy suggests a similar pathogenesis for the acute abdominal episodes. We have no adequate explanation for the excessive bleeding after tooth extraction observed in our patient.

Numerous laboratory studies were performed which were aimed at the evaluation of the patient's clotting mechanism and particularly the functional capacity of the platelets. Bleeding time done by Duke's method varied from normal up to two hours, and was not necessarily correlated with the total number of platelets. Clotting time by the Lee and White method was normal and clot retraction adequate. The determination of the prothrombin time by Quick's method was at times difficult because clumps of platelets formed prior to the clotting of the

plasma and obscured the end point. Prothrombin consumption, utilizing the method of Hirsch et al., was within normal limits. Recalcification time was normal and remained so even when plasma of this patient was made "platelet poor" by centrifuging for varying time intervals. Fibrinogen levels were determined by a modified method of Folin and Wu, and were within the upper limits of normal (200 to 400 mg. %). No increased fibrinolytic activity was manifested. Capillary fragility was normal. A hematocrit determination by Wintrobe's

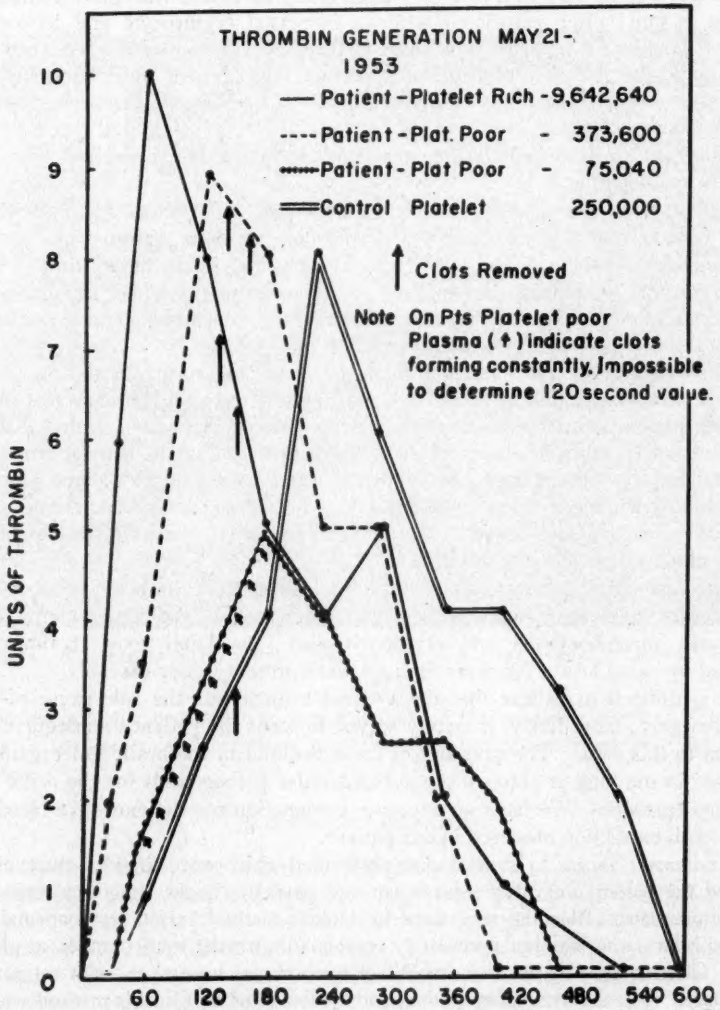

CHART 3.

method on May 21, 1953, showed the following distribution of blood elements: plasma, 55.5%; platelets, 8.5%; white blood cells, 2%; red blood cells, 34%.

The ability of the patient's blood to form clots was studied by the thrombin generation test (Pitney and Dacie) during May, 1953 (chart 3). On the basis of these examinations, which were performed repeatedly, we feel that the patient's plasma produced clots in a shorter time than does normal plasma. The peak of thrombin generation is proportional to the number of platelets.

The patient's platelets seemed to initiate the generation of thrombin as well as normal platelets. According to Pitney and Dacie, the results of the thrombin generation test may be influenced by deficiency of adequately functioning platelets, prothrombin or antihemophilic globulin. The results obtained in our study exclude the possibility of a deficiency of all of these factors.

That there may be actual qualitative variations in the blood platelets is borne out by several factors. In thrombasthenic disorders, any or several of the platelet functions may be deficient and yet the platelet count be within the range of normal. These functions, as documented by Stefanini, include: (1) capillary vasoconstriction; (2) promotion of clot retraction; (3) platelet thromboplastic activity; (4) promotion of the prothrombin to thrombin reaction; (5) enhancement of the fibrinogen to fibrin reaction; (6) inhibition of heparin. The tests most likely to show functional deficiencies of platelets are the bleeding time, clot retraction, prothrombin utilization, and thromboplastin generation. In other disturbances associated with an increased level of a heparin-like substance in the blood, platelet dysfunction has been held responsible, especially as to platelet factor 3 (antiheparinic factor).

If increased platelet adhesiveness and consequent increased thrombotic tendency are assumed in the case reported, then the cause of death is explainable. Careful microscopic scrutiny of sections of brain and lung established the presence of thrombi in these tissues. These consisted of clumped platelets intermingled with fibrin, erythrocytes and leukocytes. The changes in the brain were too acute to allow demonstrable ischemic necrosis to occur.

The cause of the bleeding tendency comprises an additional problem. We favor the thrombasthenic factor. The major abnormalities in clotting mechanism in this case were the bleeding time and clot retraction. Prothrombin consumption was unaffected. With the exception of the latter, our findings were similar to those listed by Stefanini as being the most commonly altered in states of qualitative platelet dysfunction.

Malignant tumors and leukemia are ruled out as etiologic factors in our case by the autopsy findings. The effects of splenectomy need not be seriously considered because the increase in platelets in our patient was permanent, progressive and extreme. A normal blood volume found in our patient during intervals from bleeding excludes polycythemia vera.

It remains, therefore, to consider this as a case of essential thrombocythemia, a myeloproliferative disorder analogous to leukemia or polycythemia vera.

Summary

A case of essential thrombocythemia with autopsy findings and brief review of the literature is presented. The possible mechanisms of altered platelet function, with emphasis on the probability of qualitative platelet variations, are dis-

cussed. Laboratory studies, including prothrombin consumption and thrombin generation, are presented. Our reasons for considering the condition a myeloproliferative disorder of a primary nature are listed.

Summario in Interlingua

Es presentate le caso de un patiente con excessos de sanguination occurrente post extractiones dental e persistente a vices usque a septe dies.

Le patiente habeva un historia de trauma al flanco sinistre in 1943, sequite per le apparition de un massa in le quadrante sinistro-superior. Le dimensiones del massa se augmentava gradualmente. In 1946, splenectomia esseva effectuate. Le splen pesava 2.125 g, e multiple infarcimentos esseva notate in le sectiones.

In 1952 a 1953, le patiente esseva admittite tres vices al Hospital del Administration de Veteranos, semper a causa de sanguination post extractiones dental. Le sanguination esseva tractate con mesuras local e con transfusiones de sanguine.

Le anormal constatationes laboratorial includeva un agumentate numeration de plachettas (attingente a certe tempores un nivello de 6,5 milliones per mm^3), leucocytosis amontante a circa 37.000 per mm^3 con deviation sinistrorse, e eosinophilia—a certe tempores etiam un erythrocytosis amontante a 6 milliones. Le medulla ossee monstrava un hyperplasia myeloide e megacaryocytic.

Tests effectuate pro evalutar le coagulation del sanguine in iste patiente revelava que su tempore de sanguination differeva ab le norma per usque a duo horas. Valores normal esseva constatate pro le tempore de coagulation, le retraction del coagulo, le concentration e le consumption de prothrombina, le fibrinogeno, le fibrinolysina, e le fragilitate capillar. Le resultatos del test de generation de thrombina esseva normal e proportional al numero del plachettas.

Le patiente moriva subitemente. Un meticulose studio histologic monstrava multiple thrombos in cerebro e pulmones consistente de amassate plachettas con un admixtion de fibrina, erythrocytos, e leucocytos. Le alterationes in le cerebro esseva troppo acute pro permitter le occurrentia de un demonstrabile necrosis ischemic. Tamen, micre areas de dissolution de histo esseva trovate, probabilemente como resultato de thromboses plachettal. Es includite un revista del litteratura concernite con thrombocythemia essential.

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EDITORIAL

THE AMERICAN CONGRESS OF THE INTERNATIONAL SOCIETY OF INTERNAL MEDICINE

THE meeting of internists that will take place in Philadelphia on April 23 to 26, 1958, merits worldwide attention. It will be the first American international congress devoted to all aspects of internal medicine. It is taking place in the United States at the invitation of The American College of Physicians. Although four congresses of the International Society of Internal Medicine have been held previously, all were in Europe, and although the membership already had included many other nations it was composed largely of Europeans. America was chosen for the Fifth Congress at the urgent request of the Executive Committee of the Society, and with the dual purpose of securing greater North and South American participation and of affording many of the younger and more promising physicians of other countries an opportunity to visit United States medical centers and observe their activities.

The organization of the Society was first discussed in Basel in 1947, where a group of Northern European internists had assembled at the invitation of the Switzerland Academy of Sciences. Professor A. Gigon, of Basel, and Dr. Nanna Svartz, of Sweden, were especially concerned about the project and, on subsequent enquiry, they found that many internists of other countries were similarly interested. Dr. Svartz, in the *Schweizerische Medizinische Wochenschrift* **38**: 943, 1948, referred especially to our College of Physicians as a model national organization for the presentation and discussion of all aspects of internal medicine. She felt that a similar organization on an international basis might be of significant value, from the viewpoint both of disseminating knowledge and of promoting good international relations among physicians. The Society was founded in Switzerland in 1948 with these stated objectives: "To promote scientific knowledge in internal medicine, to further the education of the younger generation and to encourage friendship among physicians in all countries."

The first president of the Society was Professor Gigon. The first Congress took place in Paris in 1950, the subsequent ones in London (1952), Stockholm (1954), and Madrid (1956). The second president was Dr. Nanna Svartz; the third and current one, Sir Russell Brain, F.A.C.P. (Hon.), of London. The membership and the number of nations represented have steadily increased. Two thousand new American members have been acquired since the announcement of the Philadelphia meeting, and now 48 nations are represented.

Eighty-one physicians from abroad will take part in the Philadelphia Congress; they will represent 27 countries. In addition to the special lec-

tures to be presented, there will be various symposia and panel discussions on arteriosclerosis, rheumatic disease, poliomyelitis, anticoagulant therapy, hematology, gastroenterology, tuberculosis, cancer, rehabilitation and heart surgery. Among the speakers at the Fifth Congress will be outstanding physicians from Russia, Hungary, Poland, Japan, South Africa, Egypt and Greece, as well as England, France, Germany and the Scandinavian countries.

At the Philadelphia Congress a special effort will be made to bring about close personal relationships among the physicians and their wives. There will be informal receptions, musical events, hospital tours and entertainment in the homes of Philadelphia families. A post-Congress tour has been organized to provide those interested an opportunity to observe several leading and representative medical institutions in Washington, Baltimore, Ann Arbor, Boston and New York, with added opportunities for general sightseeing in Washington and Niagara Falls.

A special effort is being made to have the younger internists in attendance. Many of them will be on the scientific program. Indeed, some funds have been secured to help with the travel expenses of outstanding young foreign physicians who otherwise could not come to the United States. In this, some of the national foundations and pharmaceutical organizations have been most helpful.

Although the attendance will be limited strictly to members, all qualified internists who make previous application and pay a fee of $20.00 will be included as Associate Members of the Congress. It is hoped that there will be a large attendance of Fellows of the sponsoring American College, and that their contacts with fellow physicians from other countries may lead not only to new and renewed friendships but also to improved international relations.

In addition to being sponsored by The American College of Physicians, the Congress has been aided financially and in the preparation of its program by the National Institutes of Health, the Foundation for Infantile Paralysis, the American Cancer Society, the American Trudeau Society and the Council for International Organizations of Medical Sciences.

The American College of Physicians welcomes this Congress to America, extends hearty greetings to its members, and trusts that its scientific and social program will advance the worthy objectives of the International Society of Internal Medicine.

REVIEWS

Fundamentals of Human Physiology for Students in the Medical Sciences. By W. B. YOUMANS, Ph.D., M.D. 567 pages; 14 × 22.5 cm. The Year Book Publishers, Inc., Chicago. 1957. Price, $8.50.

Dr. Youmans begins his preface ". . . I have attempted to present the fundamentals of physiology for students of the medical sciences." This has been accomplished extremely well; with brevity, authority and clarity, in a very readable fashion. The book was so impressively good that the review copy was briefly loaned to a few nurses, house officers and associates; these "students of the medical sciences" concurred with the evaluation given above.

It is a short book—567 pages—and simply cannot cover as much of the field as completely as the larger texts, nor is it of value as a reference. But, for a current and authoritative overall view of human physiology (or almost any one of its aspects) with a critical selection of references for further reading, it is, in this reviewer's opinion, without equal.

B. W. A.

A Text-Book of Surgical Pathology. 7th Ed. By CHARLES F. W. ILLINGWORTH, C.B.E., M.D., Ch.M., F.R.C.S. (Ed.), and BRUCE M. DICK, M.B., F.R.C.S. (Ed.). 730 pages; 15.5 × 24 cm. Little, Brown & Co., Boston. 1957. Price, $14.00.

The survival of this book for 24 years and seven editions convincingly testifies to its value as a guide in pathology to the students and practitioners of surgery. The authors modestly hope that this book in its seventh edition will be of value to senior students and to those preparing for senior qualifications. In this reviewer's opinion, this hope is bound to be realized.

The basic considerations of trauma and infection and host responses presented in the first three chapters serve to align the reader with important general endocrine, hemodynamic and local regenerative characteristics of surgical diseases. Metabolic phenomena and systemic reactions peculiar to specific diseases and organs are set forth in later chapters. In many instances, mention is made of the obstacles that might interrupt convalescence.

The larger part of the book is devoted to disease processes conveniently arranged according to organ and system but where practicality makes a special claim the arrangement is according to region. The gross and microscopic features by which one recognizes neoplastic, infectious, and congenital lesions are described in the text and represented by many illustrations. Controversial matters are concisely stated so that the reader is enlightened but not exhausted.

The attempt of Dr. Illingworth and Dr. Dick to include in this single volume coverage of all topics that might arise in the work of the most general of surgeons has forced upon them the necessity of brevity. To some, brevity might suggest narrow-mindedness; to others, brevity might indicate an effort to present a full measure without dross. In this book, the latter condition prevails. In either case, a bibliography is provided for those who would like to extend their investigation.

In all, this book is recommended as a handbook for the practicing surgeon and a source book for a medical school course in surgical pathology.

D. L. REIMANN, M.D.

Life Stress and Essential Hypertension: A Study Of Circulatory Adjustments in Man. By STEWART WOLF, M.D., PHILIPPE V. CARDON, JR., M.D., EDWARD M. SHEPARD, M.D., and HAROLD G. WOLFF, M.D. The Williams & Wilkins Company, Baltimore, Maryland. 1955. Price, $7.50.

In this volume the authors have set out to review the data linking circulatory adjustments to life experiences. They discuss the circulatory adjustments associated with muscular effort, the circulatory adjustments involving rhythm of the heart and peripheral vessels, and the natural history and symptomatology of essential hypertension. Much of the volume is devoted to their survey of 114 patients with essential hypertension followed for up to eight years. They were able to correlate transitory changes in the level of the blood pressure with apparently meaningful events in the life situation. They believe that the most promising therapeutic approach is toward the patient as a whole in his general life adjustment. The difficulty in the evaluation of drug and surgical therapy is stressed by the authors.

In this volume are presented some approaches to the problem of essential hypertension which are well worth the consideration of students and practicing physicians. The emphasis is rightly on the consideration of the hypertensive patient as an individual, and against the tendency to assume that the physician's responsibility to a hypertensive patient is discharged by merely prescribing a specific drug.

L. S.

Introduction to Biostatistics. By HULDAH BANCROFT, Ph.D., Professor of Biostatistics, Tulane University School of Medicine, New Orleans, La. 210 pages; 16 × 24 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1957. Price, $5.75.

This book is a revision of mimeographed notes which have assisted the author in the presentation of a series of lectures and problems in biostatistics to medical students. The particular emphasis is upon guiding the student toward a level of comprehension of statistical methods which will permit him to read medical literature in a critical manner. The exposition is intended to be in non-technical terms and presumes no knowledge of mathematics beyond elementary algebra.

The subject matter covered in this publication includes the standard areas of instruction in an introductory course in biostatistics. Chapters on classification of data and on tabular and graphical presentation are well done. There follow then chapters on statistical methods for quantitative data, statistical methods for enumerative data, and a brief discussion of sampling. The content of the chapter on sampling particularly in connection with the presentation of the concept of the β type error, in the opinion of this reviewer, requires considerable revision. Issues of bias and definition of terms would best be discussed in the earliest pages of the text. The method for selecting samples, say in community morbidity surveys might be more meaningful in the student's appreciation of statistical method than an abbreviated discussion of the mechanics of determining sample size from a consideration of α and β errors.

In the latter part of this text, individual chapters are devoted to the Chi Square Test, Correlation and Regression, Life Tables and to Bioassay. In general, these subjects are treated in clear and comprehensible form. One would think that the Litchfield-Wilcoxin method for estimation in bioassay would better serve to demonstrate the nature of this subject to medical students than the Reed-Muench technic, the only one presented.

For medical students and physicians interested in understanding the methods involved in determining basic statistical descriptive indexes, this publication will serve as a useful reference text. However, this book requires some revision before

it can be unqualifiedly recommended as a basis for stimulating and inviting the interest of the reader in the problems of statistical inference and in critical evaluation of medical literature.

MATTHEW L. TAYBACK, Sc.D.

The Teaching of Hygiene and Public Health in Europe: A Review of Trends in Undergraduate and Post-Graduate Education in Nineteen Countries. World Health Organization Monograph Series No. 34. By F. GRUNDY, M.D., M.R.C.P., D.P.H., and J. M. MACKINTOSH, M.D., LL.D., F.R.C.P., D.P.H.; with an introduction by JACQUES PARISOT. 254 pages; 16 × 24 cm. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. 1957. Price, $5.00 (cloth).

This monograph by two veteran teachers of preventive medicine and public health is based on two WHO conferences, one held in Nancy, France in 1952 on European teaching of hygiene to medical students and the other held at Göteborg, Sweden, in 1953 on the postgraduate training of physicians and other public health workers for career work in this field. The first chief sections of the volume deal separately with these undergraduate and postgraduate parts of the subject, and they are followed by a section which gives the details of the curricula in both fields in 19 individual European countries.

The difficult task of arousing the interest of the medical student so that in his practice he will not confine himself to curative medicine but will play his part in preventive and community medicine is given serious consideration. Just as the doctor in general practice should be an adviser on health and sickness to the family as a whole, so the health officer should be a general adviser on health to the community, an organizer of civic preventive medicine and a team leader in his jurisdiction.

The interrelations between the scope and subjects of instruction in hygiene for the medical student and for the postgraduate physician are important and are discussed. It would seem that this monograph will be of interest and value to deans of medical schools and schools of public health and to all on their faculties who play a part in the present-day teaching of hygiene or preventive medicine. The volume may be secured from the Columbia University Press, International Documents Service, 2960 Broadway, New York 27, N. Y.

H. W.

Essays in Metabolism: The John Punnett Peters Number of the Yale Journal of Biology and Medicine. Edited by LOUIS G. WELT, M.D., Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill. 382 pages; 17 × 26 cm. Little, Brown & Co., Boston. 1957. Price, $6.50.

It is probably true that the currently very popular fields of clinical physiology and clinical biochemistry owe more to the work, the teaching, and the writing of Dr. John P. Peters than to those of any other man. Dr. Peters died on December 29, 1955; and in this memorial volume, former students have prepared ten essays covering half a dozen subjects that their former teacher had made his own.

All of the authors are acknowledged authorities and they present the current picture of a subject they are currently investigating. A notable feature of each article is an excellent bibliography.

The general areas covered are in the fields of water and electrolyte metabolism, acid base balance, carbohydrate and lipid metabolism.

As might be expected, each paper emphasizes basic principles and fundamental mechanisms; therapeutics and other clinical implications are left to the abilities of the readers to use these concepts as tools.

B. W. A.

Ten Million and One. Neurological Disability as a National Problem. (A multiple author book resulting from a conference sponsored by the National Health Council.) 102 pages; 14 × 21 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, N. Y. 1957. Price, $3.50.

This book results from the Conference on Neurologic Disability as a National Problem held at Arden House, Harriman, N. Y., in December 1955. The conference was sponsored by the National Health Council. Its professed aim was to consider neurologic disabilities as one problem, rather than in a piecemeal fashion, and to discuss methods of mobilizing community resources to solve this problem, as well as the best methods of reaching a solution. Participants included chiefly representatives of voluntary health organizations but various professional health organizations also were represented. Topics considered included the economic aspects of neurologic disability as a national problem, professional and technical management of the problem, the problem of dissemination of information regarding the problem, research, and education of the neurologically disabled.

Besides presenting the nature of the problem in a succinct and terse fashion, this volume contains much information concerning the avenues through which a solution may be approached. Although the information is of no value to the physician in the management of the individual neurologic patient, it is of interest to all persons, both professional and lay, involved or interested in the care of the neurologically disabled.

CHARLES VAN BUSKIRK, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

L'Arthrographie Opaque du Genou: Contribution au Diagnostic des Dérangements Internes du Genou. Par PAUL FICAT; préface du Pr R. MERLE D'AUBIGNÉ. 243 pages; 25 × 16.5 cm. 1957. Masson & Cie., Paris. Price, 3.800 fr.

Atomic Energy in Medicine. By K. E. HALNAN. 157 pages; 22.5 × 14 cm. 1957. Philosophical Library, New York. Price, $6.00.

Autonomic Imbalance and the Hypothalamus: Implications for Physiology, Medicine, Psychology, and Neuropsychiatry. By ERNST GELLHORN, M.D., Ph.D., Professor of Neurophysiology, University of Minnesota. 300 pages; 24 × 15.5 cm. 1957. University of Minnesota Press, Minneapolis. Price, $8.50.

Cardiovascular Rehabilitation: Report of a Conference Held at the New York University-Bellevue Medical Center, New York, May 25 to 27, 1956, under the Sponsorship of the Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, and Supported by a Grant from The National Heart Institute, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare. Edited by PAUL DUDLEY WHITE, M.D., Massachusetts General Hospital, Boston; HOWARD A. RUSK, M.D., Director, Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York; BRYAN WILLIAMS, M.D., Clinical Instructor in Medicine, Southwestern Medical School, University of Texas, Dallas; and PHILIP R. LEE, M.D., Department of Internal Medicine, Palo Alto Clinic, Palo Alto, California. 155 pages; 21 × 14 cm. 1957. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $6.50.

Chemical Methods in Clinical Medicine: Their Application and Interpretation with Techniques of Simple Tests. 4th Ed. By G. A. HARRISON, B.A., M.D., B.Ch. (Cantab.), M.R.C.S. (Eng.), L.R.C.P. (Lond.), F.R.I.C., Consultant Pathologist to the South West Metropolitan Regional Hospital Board at St. Richard's, The Royal West Sussex and Graylingwell Hospitals, Chichester, Sussex, etc. 667 pages; 24 × 15.5 cm. 1957. Grune & Stratton, New York. Price, $11.00.

Cortisone Therapy, Mainly Applied to the Rheumatic Diseases. By J. H. GLYN, M.A. (Cantab.), M.D., M.R.C.P., D.Phys. Med., Consultant in Physical Medicine to the Prince of Wales and Tottenham Group of Hospitals. 162 pages; 22.5 × 14 cm. 1957. Philosophical Library, Inc., New York. Price, $10.00.

Deafness, Mutism and Mental Deficiency in Children. By LOUIS MINSKI, M.D., F.R.C.P., D.P.M., Consultant Psychiatrist Royal National Throat, Nose and Ear Hospital, etc. 82 pages; 19 × 12.5 cm. 1957. Philosophical Library, Inc., New York. Price, $3.75.

Diabète Sucré, Diabète Insipide, Régulation Électrolytique. Colloque d'Endocrinologie 1957. Rapports de la IV^e Réunion des Endocrinologistes de Langue Française, Paris, 27–28–29 Juin 1957. Publiés par les soins du PROFESSEUR A. SOULAIRAC. 420 pages; 25 × 16 cm. 1957. G. Doin & Cie. and Masson & Cie., Paris. Price, 3.800 fr.

Disorders of the Blood: Diagnosis: Pathology: Treatment: Technique. 8th Ed. By SIR LIONEL E. H. WHITBY, C.V.O., M.D., M.A., M.D. (Cantab.), F.R.C.P. (Lond.), D.P.H., Late Regius Professor of Physic in the University of Cambridge, etc.; and C. J. C. BRITTON, M.D. (New Zealand), D.P.H., Physician and Haematologist to the Prince of Wales's Hospital, London, etc. 878 pages; 25 × 16 cm. 1957. Grune & Stratton, New York. Price, $11.50.

Eisen, Kupfer und Eiweiss am Beispiel der Leberkrankheiten. Von PRIV.-DOZ. DR. J. LANGE; mit einem Geleitwort von PROF. DR. PAUL MARTINI. 89 pages; 24 × 17 cm. (paper-bound). 1958. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, kartoniert DM 13.50.

Expert Committee on Malaria: Sixth Report. World Health Organization Technical Report Series No. 123. 84 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Fieber Unspezifische Abwehrvorgänge Unspezifische Therapie. Von PROF. DR. FERDINAND HOFF. 145 pages; 21.5 × 15 cm. 1957. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 16.50.

The Incurable Wound, And Further Narratives of Medical Detection. By BERTON ROUECHÉ. 177 pages; 21 × 14 cm. 1957. Little, Brown and Company, Boston. Price, $3.50.

International Sanitary Regulations Adopted by the Fourth World Health Assembly in 1951 and Amended by the Eighth and Ninth World Health Assemblies in 1955 and 1956. Annotated Edition. 129 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, $1.00.

Joint FAO/WHO Expert Committee on Milk Hygiene: First Report. World Health Organization Technical Report Series No. 124. 54 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Juvenile Epilepsy: Report of a Study Group. World Health Organization Technical Report Series No. 130. 44 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Mises au Point Obstétricales et Gynécologiques. Sous la direction de M. LACOMME; par J. BRET, R. DEUIL, P. GELLÉ, M. LANVIN, G. LE LORIER, P. MAGNIN, P. MAURICE et P. THIROLOIX, P. MORIN, P. VIGNES. 136 pages; 25 × 17 cm. (paper-bound). 1957. Masson & Cie., Paris. Price, 1.600 fr.

Nierenkrankheiten: Physiologie, Pathophysiologie, Klinik und Therapie. Von HANS SARRE. 540 pages; 24.5 × 18 cm. 1958. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 59.–

The Normal Child: Some Problems of the First Five Years and Their Treatment. 2nd Ed. By RONALD S. ILLINGWORTH, M.D. (Leeds), F.R.C.P. (Lond.), D.P.H., D.C.H., Professor of Child Health, The University of Sheffield, etc. 356 pages; 24 × 16 cm. 1957. Little, Brown and Company, Boston. Price, $7.00.

Ophthalmology and Otolaryngology. Surgery in World War II. Medical Department, United States Army. Editor in Chief: COLONEL JOHN BOYD COATES, JR., MC; Editor for Ophthalmology: M. ELLIOTT RANDOLPH, M.D.; Editor for Otolaryngology: NORTON CANFIELD, M.D.; Associate Editor: ELIZABETH M. MCFETRIDGE, M.A. 605 pages; 25.5 × 18 cm. 1957. Office of the Surgeon General, Department of the Army, Washington, D. C. Price: For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. Price, $5.00 (buckram).

Pediatric Profiles (Reprinted from *The Journal of Pediatrics,* November, 1954–November, 1957). BORDEN S. VEEDER, Editor. 267 pages; 26 × 17.5 cm. 1957. The C. V. Mosby Company, St. Louis. Published for subscribers to *The Journal of Pediatrics*—not for sale.

Psychosomatics: A Series of Five Lectures. Published under the auspices of The Netherlands Society for Psychiatry and Neurology as Supplement No. 3 to the *Journal Folia Psychiatrica, Neurologica et Neurochirurgica Neerlandica.* Edited by JOH. BOOIJ. 125 pages; 23 × 15.5 cm. 1957. Elsevier Press, Inc., Houston, Texas. Price, $5.00.

La Rauwolfia: Chimica, Farmacologia ed Applicazioni Cliniche. By LIVIO MECIANI. 582 pages; 22 × 15.5 cm. (paper-bound). 1957. Casa Editrice Ambrosiana, Milan.

The Relation of Psychiatry to Pharmacology. By ABRAHAM WIKLER, M.D., National Institute of Mental Health, Addiction Research Center, Department of Health, Education, and Welfare, Public Health Service Hospital, Lexington, Kentucky. 322 pages; 25.5 × 17.5 cm. (paper-bound). 1957. Published for the American Society for Pharmacology and Experimental Therapeutics by The Williams & Wilkins Company, Baltimore. Price, $4.00.

Rhythmusstörungen des Herzens: Systematik. Ursache und Klinische Bedeutung Therapie. Von KONRAD SPANG. Mit Beiträgen: *Die Morphologie des Reizleitungssystemes, Ihre Orthologie und Pathologie* von PROF. DR. MED. W. DOERR; *Physiologie der Herzirregularitäten* von PRIV.-DOZ. DR. W. TRAUTWEIN. 548 pages; 28.5 × 20 cm. 1957. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 148.–

Shock and Circulatory Homeostasis: Transactions of the Fifth Conference, November 30, December 1, and 2, 1955, Princeton, N. J. Edited by HAROLD D. GREEN, M.D., D.Sc., Professor of Physiology and Pharmacology and Associate in Internal Medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C. 337 pages; 23.5 × 15.5 cm. 1957. Sponsored by Josiah Macy, Jr. Foundation, New York. Price, $4.75.

Transactions, American Society for Artificial Internal Organs. Volume III, Chicago, Illinois, April 14–15, 1957. 95 pages; 28 × 21.5 cm. (loose-leaf, paper bound). 1957. American Society for Artificial Internal Organs, Georgetown University Medical Center, Washington, D. C. Price, $3.00.

Treatment and Care of Drug Addicts: Report of a Study Group. World Health Organization Technical Report Series No. 131. 19 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Les Urétrites non Gonococciques. Bibliothèque de L'Union Internationale Contre le Péril Vénérien et les Tréponématoses. No. 1. Par S. AMBROSE, G. AUCKLAND, H. BAUER, J. BRISOU, H. P. CHU et W. I. B. BEVERIDGE, F. COSTE et M. BOUREL, L. DIENES et R. L. BERG, P. DUREL et A. SIBOULET, A. H. HARKNESS et S. R. M. BUSHBY, E. KLIENEBERGER-NOBEL, A. MIDANA et F. SERRI, M. RUITER, M.C. SHEPARD, CL. SOREL, PH. THYGESON, R. TULASNE et R. MINCK, R. R. WILLCOX; avec la collaboration de A. DARBON, D. G. ff. EDWARD, H. JAEGER, G. JAYLE, S. MADOFF. Secrétaire de la Rédaction: P. DUREL. 102 pages; 27 × 21.5 cm. (paper-bound). 1957. Masson et Cie., Paris. Price, 1.600 fr.